CHAPTER 28

Ebola Virus Disease and Hemorrhagic Fevers

Christopher A. Sanford, Timothy E. West, and Shevin T. Jacob

HEMORRHAGIC FEVERS

Overview and Transmission

Hemorrhagic fevers are caused by infection with single-stranded, small RNA viruses in the Arenaviridae, Filoviridae, Bunyaviridae, or Flaviviridae families (**Table 28.1**). The clinical picture is usually one of hemodynamic instability and coagulation abnormalities leading to bleeding.

The viruses are primarily zoonotic, existing in mammalian reservoirs. Humans may become infected by interaction with the reservoir or via an arthropod vector. While human-to-human transmission may occur with certain viruses and contribute to epidemics (with the exception of dengue), humans are not considered reservoirs. Therefore, infection primarily occurs in geographic locales that support the reservoir or the vector. However, all inhabited continents and climates host these viruses (**Table 28.1**). In light of the recent epidemic of Ebola virus disease (EVD), special attention is given to this infection below. Yellow fever and dengue are discussed in other chapters.

Clinical Manifestations

The many different viruses that cause viral hemorrhagic fever (VHF) can result in a variety of clinical presentations. Early disease or mild infection can be nonspecific and potentially confused with respiratory viruses, hepatitis, gastroenteritis, primary human immunodeficiency virus, malaria, sleeping sickness, bacterial sepsis, or other infections. A variety of types of rash may be seen. In Lassa fever, the pharynx may be erythematous or exudative. Bleeding may not be overt and may be delayed; however, more severe disease may be characterized by bleeding, capillary leak, or shock. Laboratory findings may be variable but are often suggestive of disseminated intravascular coagulopathy. In severe disease, there may be pronounced electrolyte and acid-base disturbances.

Diagnosis

A high level of clinical suspicion for VHF in individuals who may have been exposed to reservoirs or vectors of infection is required. Confirmation of infection generally requires detection of viral antigen or RNA. These tests are performed in specialized laboratories; commercial kits for diagnosis are not currently available. Serology may be useful in the convalescent phase of illness. It is important to exclude other causes of infection.

Treatment

While there is substantial variation in the pathogenicity of the viruses, care of the patient with VHF is primarily supportive. Diligent organ support including correction of hypovolemia and electrolyte abnormalities, management of hemorrhage and coagulation derangements, mechanical ventilation, and renal replacement therapy has the potential to markedly

TABLE 28.1 Hemorrhagic Fever Viruses in Humans

Family	Virus	Disease	Main Reservoir or Vector	Geographic Distribution of Disease
Arenaviridae	Lassa	Lassa fever	Rodent (multimammate rat, or *Mastomys natalensis*)	West Africa
	Lujo	Lujo hemorrhagic fever	Unknown; presumed rodent	Zambia
	Junin	Argentine hemorrhagic fever	Rodent (corn mouse, or *Calomys musculinus*)	Argentine Pampas
	Machupo	Bolivian hemorrhagic fever	Rodent (large vesper mouse, or *Calomys callosus*)	Beni Department, Bolivia
	Guanarito	Venezuelan hemorrhagic fever	Rodent (cane mouse, or *Zygodontomys brevicauda*)	Portuguesa State, Venezuela
	Sabiá	Brazilian hemorrhagic fever	Unknown; presumed rodent	Rural area near São Paulo, Brazil?
	Chapare	Chapare hemorrhagic fever	Unknown; presumed rodent	Cochabamba, Bolivia
Filoviridae	Ebola	Ebola hemorrhagic fever	Unknown; fruit and insectivorous bat species have been implicated	Sub-Saharan Africa
	Marburg	Marburg hemorrhagic fever	Fruit bat (Egyptian fruit bat, or *Rousettus aegyptiacus*; perhaps others)	Sub-Saharan Africa

Bunyaviridae	Hantaan, Seoul, Puumala, Dobrava-Belgrade, others	Hemorrhagic fever with renal syndrome	Rodent (Hantaan: striped field mouse, or *Apodemus agrarius*; Seoul: Norway rat, or *Rattus norvegicus*; Puumala: bank vole, or *Clethrionomys glareolus*; Dobrava-Belgrade: yellow-necked field mouse, or *Apodemus flavicollis*)	Hantaan: northeast Asia Seoul: urban areas worldwide Puumala and Dobrava-Belgrade: Europe
	Sin Nombre, Andes, Laguna Negra, others	Hantavirus pulmonary syndrome	Rodent (Sin Nombre: deer mouse, or *Peromyscus maniculatus*; Andes: long-tailed rat, or *Oligoryzomys longicaudatus*; Laguna Negra: vesper mouse, or *Calomys laucha*)	Sin Nombre: North America, Andes Laguna Negra: southern South America
	Rift Valley fever	Rift Valley fever	Domestic livestock/mosquito (*Aedes* and others)	Sub-Saharan Africa, Saudi Arabia, Yemen
	Congo-Crimean hemorrhagic fever	Congo-Crimean hemorrhagic fever	Wild and domestic vertebrates/tick (primarily *Hyalomma* species)	Africa, Balkans, southern Russia, Middle East, India, Pakistan, Afghanistan, western China
Flaviviridae	Yellow fever	Yellow fever	Monkey/mosquito (*Aedes aegypti*, other *Aedes* and *Haemagogus* spp.)	Sub-Saharan Africa, South America up to Panama
	Dengue	Dengue hemorrhagic fever	Human/mosquito (*A. aegypti* and *Aedes albopictus*)	Tropics and subtropics worldwide
	Kyasanur Forest disease	Kyasanur Forest disease	Vertebrate (rodents, bats, birds, monkeys, others)/ tick (*Haemaphysalis* species and others)	Southern India; Yunnan Province, China; Saudi Arabia
	Omsk hemorrhagic fever	Omsk hemorrhagic fever	Rodent/tick (primarily *Dermacentor* and *Ixodes* species)	Western Siberia

Adapted from Bausch, D.G., 2011. Viral hemorrhagic fevers. In: Goldman's Cecil Medicine, twenty-fourth ed. Saunders Elsevier, Philadelphia, pp. 2147–2155.

reduce death rates. For specific infections, including Lassa fever, hemorrhagic fever with renal syndrome, South American hemorrhagic fevers, and Crimean-Congo hemorrhagic fever, ribavirin, a purine nucleoside, may be considered, but robust data regarding its efficacy are lacking. Post-exposure vaccination, passive immunotherapy, and novel immunomodulatory agents are largely experimental but may carry some benefit. Suspected or confirmed co-infection should also be treated.

EBOLA VIRUS DISEASE

Overview and Transmission

Ebolavirus was discovered in 1976 near the Ebola River in what was then Zaire (now Democratic Republic of Congo). Ebola is one of three known filoviruses; the other genera within the family Filoviridae are *Marburgvirus* and, more recently discovered, *Cuevavirus*. Five species of the genus *Ebolavirus* have been identified: *Sudan ebolavirus*, *Zaire ebolavirus*, Tai Forest (Ivory Coast) *ebolavirus*, *Reston ebolavirus*, and *Bundibugyo ebolavirus*. *Bundibugyo*, *Zaire*, and *Sudan* have caused large outbreaks in Africa. *Z. ebolavirus* is the cause of the epidemic that began in West Africa in December 2013. *R. ebolavirus* is not pathologic in humans.

While transmission from a zoonotic reservoir is suspected, no definitive link between animal species and transmission of Ebola to human beings has been made. Some evidence suggests fruit bats, family Pteropodidae, as the natural reservoir, but other studies including recent work from the West African Ebola outbreak implicate an insectivorous bat species, *Mops condylurus*. Ultimately, the primary mode of transmission of Ebola virus into humans remains unknown.

In humans, the majority of *Ebolavirus* transmission is via contact with bodily fluids of symptomatic patients. It is not known to be transmitted by eating food (with the exception of handling bush meat), by drinking water, or via the bites of mosquitoes or other insects. *Ebolavirus* RNA has been identified in the blood, breast milk, semen, vaginal fluid, placental/amniotic fluid, skin/sweat, saliva, eyes, urine, and feces of infected individuals. Detection of viral RNA, however, does not indicate infectiousness, whereas viral isolation through culture is more suggestive. Of the bodily fluids and sites where viral RNA has been detected, blood, breast milk, saliva, aqueous fluid, urine, and semen have yielded cultured virus. Regarding human-to-human transmission of Ebola virus from sexual fluids or other routes (e.g., airborne), limited data exist, and epidemiologic patterns reported during outbreaks have not supported these types of transmission playing a major role in outbreak transmission dynamics.

Epidemics begin when the human index case either has contact with a reservoir species or when transmission of an infection to a person by a blood-borne mechanism occurs during activities such as preparing the meat of wild animals (also called bushmeat), which have become exposed and infected with Ebola virus.

Amplification of human-to-human transmission in the community has been linked to burial practices common to indigenous groups throughout Africa, in which family and community members prepare the dead body. A study on deceased Ebola-infected macaques found that viable virus could be recovered for at least 7 days after death. Also, transmission of Ebola virus by health workers not suspecting EVD in a symptomatic patient for whom they provided care has been an important cause of both community and nosocomial amplification of the outbreak.

In the first 9 months of the West African outbreak, an average incubation period of 11.4 days was observed. Symptom onset after exposure is under 21 days in 95% of patients (which is the recommended follow-up period for contacts).

Given that Ebola is a zoonosis, its eradication is unlikely.

Epidemiology and Outbreaks

Prior to the West African outbreak that began in late 2013, the largest outbreak of Ebola was in Uganda in 2000, with 425 cases. In that epidemic the case fatality rate was 53%.

Between 1967, when Marburg virus was first identified, and 2011, there were 30 outbreaks of either Ebola or Marburg hemorrhagic fever, totaling almost 2500 cases.

Almost all outbreaks of Ebola prior to 2014 were rural. Two urban outbreaks did occur, in Kikwit, Zaire, population 400,000, in 1995, and in Gulu, Uganda, population 100,000, in 2001; each caused about 250 deaths.

One group at markedly elevated risk for infection with Ebola is healthcare workers. As of early May 2015, more than 850 healthcare workers have been infected with Ebola in current epidemic, of whom almost 60% have died.

The largest outbreak of Ebola began in December 2013 in the Guéckédou and Macenta districts of Guinea. The outbreak, however, was not identified as Ebola until the spring of 2014. By that time, cases had also been reported across the border in neighboring Liberia. Unconfirmed cases were also reported around that time in neighboring Sierra Leone, but the first officially diagnosed case of EVD was not reported until May 2014. On August 8, 2014, the World Health Organization (WHO) declared the epidemic to be a "public health emergency of international concern." As of May 10, 2015, the West African EVD outbreak has resulted in almost 27,000 cases reported in Guinea, Liberia, Sierra Leone, Mali, Nigeria, Senegal, Spain, United Kingdom, and United States. The overall reported case fatality rate is 41.4% and varies considerably depending on the country and across sites within countries.

As of May 2015, there have been 11 cases of Ebola in the United States: seven were evacuated to the United States from West African countries, and four were first diagnosed in the United States (two of which were contracted in the United States). Two (18%) of these 11 patients died.

Clinical Manifestations

In general, patients with Ebola have a somewhat predictable clinical course (Chertow et al. 2014). During the first couple days of infection, patients present with a mild fever, decreased appetite, and headache. During this time, patients are ambulatory and generally able to drink and eat. Over the next 2-3 days, fever increases (as high as 40° C), headache continues with onset of arthralgias and myalgias, and mild gastrointestinal symptoms arise, including anorexia, nausea, onset of diarrhea (two to three bowel movements daily), epigastric pain, and occasionally hiccups. During these first 3-4 days of illness, patients may still be ambulating; clinicians should monitor for the onset of asthenia and lassitude.

For patients whose illness progresses beyond this stage, a severe gastroenteritis phase ensues with increased diarrhea (reported up to 10 L daily in some cases) and vomiting; hematemesis and bloody diarrhea can be seen in a minority of cases. During this phase, manifestation of signs of systemic involvement and shock can be seen, including tachycardia and hypotension, conjunctival injection, chest pain, dysphagia, decreasing urine output, and little to no ambulation. In addition, a subset of patients experience an encephalopathic/encephalitic phenotype with delirium (both hypoactive and hyperactive), manifested by confusion, impaired cognition, agitation, and, less commonly, seizures. It is uncertain whether these central nervous system sequelae are secondary to direct cytopathic injury from the Ebola virus, electrolyte disarray, or a combination of both.

The gastrointestinal phase lasts for approximately 5 days, after which a convalescent or terminal phase ensues. During this phase, fever and gastrointestinal symptoms subside, generally corresponding with a decrease in Ebola viral load. Many patients recover during this period. Some patients, however, will have suffered from end-organ damage with oliguria/anuria and progression to coma. While primary hypoxia is uncommon, end-stage cases may also manifest tachypnea and respiratory distress likely to represent respiratory compensation for metabolic acidosis developed as a result of shock and acute kidney injury. Patients in this terminal phase may require higher levels of supportive care (e.g., mechanical ventilation and hemodialysis) without which many of these patients will succumb to their illness.

On physical exam, rash is reported in 25-52% of clinical reports; it is often nonpruritic, erythematous, and maculopapular and may be difficult to discern in dark-skinned individuals.

Other exam findings may include hyperemic conjunctivae, pharyngeal erythema, enlarged lymph nodes, and tender hepatomegaly with the edge of the liver palpable below the ribcage.

Other conditions to consider in patients presenting with nonspecific symptoms concerning for Ebola include bacterial sepsis, other hemorrhagic fevers (such as Crimean-Congo hemorrhagic fever, Lassa fever, Marburg hemorrhagic fever, and dengue hemorrhagic fever), dysentery, malaria, typhoid fever, hepatitis, cholera, rickettsioses, and leptospirosis.

The majority of EVD patients have been cared for in sub-Saharan Africa where collection of clinical laboratory data is rare. Nonetheless, some insight has been gained through minimal data from various outbreaks and newer clinical data from EVD patients who have been evacuated to higher resource settings. A common feature of patients with EVD is leukopenia at time of presentation, with a reduced number of lymphocytes and an increased proportion of granulocytes. As the illness progresses, the total white cell count can rise above normal, with an increase in immature granulocytes and the appearance of atypical lymphocytes. Thrombocytopenia is often present at during the patient's clinical course and can decline to very low levels in more severe cases.

Metabolic derangement is also common with the excessive gastrointestinal losses. Renal function is often normal at time of presentation, but acute kidney injury is common with oliguria and anuria occurring in severe cases. Related electrolyte abnormalities include hypo- and hypernatremia due to fluid and sodium losses and fluid shifts from diarrhea and vomiting. Hypokalemia is also common from potassium loss in diarrhea, but hyperkalemia can also occur, especially in patients with severe acute kidney injury.

Liver enzymes are often abnormal with a disproportionate elevation in aspartate aminotransferase (AST) over alanine aminotransferase. Creatinine kinase can also be elevated, consistent with mild rhabdomyolysis and perhaps suggesting a dual liver and muscle source for the elevated AST level. When tested, partial thromboplastin time is more commonly prolonged than prothrombin time, and bilirubin levels are usually within normal limits. Though described as being a pathogenic feature in some nonhuman primate models, disseminated intravascular coagulation has not been reported commonly in human cases of EVD, likely because of lack of tests to measure for it.

Patients who die of Ebola more commonly progress from prostration and obtundation to hypotension and shock to coma. Some deaths, however, occur suddenly, perhaps resulting from dysrhythmias in the setting of electrolyte derangements. Most deaths occur between days 7 and 12 of illness, with a median survival of 9 days from symptom onset to death. The mean time from admission to hospital to death in the current West African epidemic is 4.2 days.

Independent risk factors for mortality reported from different cohorts include elevated Ebola viral load at the time of admission, increased age (>40 years), and end-organ damage, particularly involving the liver and kidneys. Other factors observed to be associated with a high mortality include age <2 years, pregnancy, and hemorrhage. Historically, case fatality rates have ranged from 25 to 90%. In the first 9 months of the 2014 West African outbreak, a case fatality rate (CFR) of 71% was observed with a decline to around 55% later in the epidemic. The reason for the decreased CFR is unclear but likely attributable to increased availability of safe facilities and decreased time to seeking care by patients and their families in the community.

At approximately day 10 of illness, about 40% of patients begin to improve. Patients who live to day 13 of illness have a higher likelihood of surviving. Current recommendations for discharge criteria include ≥3 days without fever or any significant symptoms (e.g., diarrhea, vomiting, bleeding), significant improvement in clinical condition, ability to perform activities of daily living, and a negative blood polymerase chain reaction (PCR) test for Ebola virus on the third day of being asymptomatic. If the PCR test remains positive despite lack of symptoms, current recommendations are to repeat PCR in 48 hours and counsel patients that the PCR test can take several days to become undetectable despite resolution of symptoms.

In survivors, convalescence is prolonged, lasting weeks to months. Common signs and symptoms reported during convalescence include asthenia, weight loss, headache, dysesthesias, migratory arthralgias, sloughing of skin, and loss of scalp hair. Survivors have also reported blurred or partial loss of vision, dizziness, headache, insomnia, and myalgia.

Diagnosis

The CDC defines a "person under investigation" for Ebola as someone with both (1) a history of exposure (travel to a country with widespread Ebola transmission or contact with a person with confirmed Ebola) within the past 21 days and (2) signs and symptoms potentially consistent with Ebola (fever, either subjective or ≥100.4° F [38° C], or headache, weakness, muscle pain, vomiting, diarrhea, abdominal pain, or hemorrhage). Similarly, the WHO identifies a suspect case as one of the following: any person (1) having had contact with a clinical case and presenting with an acute fever (>100.4° F [38° C]); (2) having had contact with a clinical case and presenting with three or more of the following symptoms: headache, generalized or articular pain, intense fatigue, nausea or vomiting, loss of appetite, diarrhea, abdominal pain, difficulty in swallowing, difficulty in breathing, hiccups, miscarriage; (3) presenting with acute fever and three or more of the above-mentioned symptoms; (4) with unexplained bleeding or miscarriage; and (5) who has an unexplained death. Across outbreaks, the case definition may require refinement depending on epidemiologic data specific to a particular outbreak. To improve the performance of existing case definitions for identification of suspect cases during the West African outbreak, clinical data from one Ebola Treatment Unit in Liberia were used to develop a clinical prediction score that could help determine whether a person has EVD. The Ebola Prediction Score comprised six independent predictors (having a sick contact, diarrhea, loss of appetite, muscle pain, difficulty swallowing, and absence of abdominal pain).

Establishing a diagnosis of Ebola ultimately requires isolation of Ebola virus, viral antigen capture, or virus-specific antibody from a bodily fluid sample. In settings where diagnostic capacity exists, the most commonly utilized test for diagnosing Ebola is real-time reverse transcription PCR (RT-PCR). Persons with Ebola are not known to be viremic during the incubation period; however, virus has been detected in blood samples on the day of symptom onset. A negative PCR test obtained on a patient who has had symptoms of <72 hours' duration may represent a false negative test. Tests obtained before 72 hours of symptoms should be repeated at or after 72 hours after onset of symptoms if there is ongoing clinical suspicion of EVD. Diagnosis of Ebola in deceased patients can be made using PCR testing of blood (often collected by cardiac puncture) or a sample collected by oral swab. If appropriate biosafety facilities are available, immunohistochemistry testing and virus culture can also be utilized.

Ebola is usually undetectable in the blood by the end of the second week. In survivors, however, infectious virus may persist in some immune privileged anatomic sites, including the testes and eyes. Later in the course of the disease (around day 10) or after recovery, evidence of current or past Ebola infection can be detected by virus-specific immunoglobulin (IgM and IgG antibodies). Most fatal cases fail to mount an antibody response. Hence, detecting virus-specific immunoglobulin in serum is a favorable finding. Virus-specific IgG has been detected in survivors as long as 11 years after infection.

Recent development of an antigen-based rapid diagnostic test for Ebola has been a promising addition to the arsenal of EVD diagnostics in light of its good performance characteristics (92% sensitivity, 85% specificity) and rapid turn-around time of 15 minutes. Further validation is required, however, before it formally can be used as a diagnostic in an outbreak.

Treatment

Despite the use in high-resource settings of investigational therapies (see below), the mainstays of treatment in both high- and low-resource settings are aggressive fluid replacement, electrolyte repletion, antiemetics, antimicrobials to treat co-infections, analgesia and

antipyretics, nutrition, and targeted organ support. In the United States, the lower fatality rate of 18% seen in the first 11 cases suggests that even critically ill patients with end-organ damage can survive with aggressive treatment that, when necessary, may include mechanical ventilation and hemodialysis.

During an outbreak such as the West African Ebola outbreak, triaging patients by severity of illness enables health workers to appropriately manage and treat high volumes of patients. For example, Chertow et al. (2014) recommend the following three triage categories:

1. Clinically hypovolemic, not in shock, and able to provide self-care
2. Clinically hypovolemic, not in shock, not able to provide self-care
3. In shock with evidence of organ failure whose outcome would not be altered by available medical intervention.

For those patients falling in the first category, priority should be placed on encouragement of oral rehydration salts and nutrition complemented by symptomatic treatment such as oral analgesics, antinausea, and antiemetic medications.

A proportion of patients from group 1 will inevitably progress to group 2, and other patients may be presenting to the treatment unit at this level of severity. Health workers should be trained to identify early those patients who are beginning to deteriorate by monitoring for increased gastrointestinal losses, decreased ability for self-care, lethargy, and lassitude. Once identified as entering into group 2, these patients should immediately receive short-term intravenous therapy aimed to match gastrointestinal losses and electrolyte replacement, if capacity for electrolyte monitoring is available. Importantly, being able to establish intravenous access, deliver adequate volume of fluids, and safely manage needles and devices requires appropriate staff and triage planning to ensure that the sickest patients receive the necessary care. In addition, broad-spectrum antibiotics are often administered for prophylaxis against pathogenic translocation of intestinal bacteria in severely ill patients and for empiric treatment of non-Ebola diarrhea and pneumonia (especially in children).

In addition to supportive care, a number of investigational therapeutics have been developed or repurposed for treatment of EVD. During the West African Ebola outbreak, a number of these therapeutics were used under compassionate use, particularly in patients who were repatriated to either the United States or United Kingdom. These therapeutics include (1) ZMapp (and a related drug called ZMab), a combination of three different monoclonal antibodies that bind to the protein of the Ebola virus; (2) brincidofovir, a lipid-conjugated version of cidofovir, an oral nucleotide analog with broad-spectrum in vitro antiviral activity; (3) favipiravir, a broad-spectrum antiviral compound with activity against RNA viruses; and (4) TKM-Ebola, a combination of small interfering RNAs targeting several proteins in the RNA virus. Additionally, convalescent whole blood and plasma transfusions from patients who have recovered from Ebola have been administered. Though the efficacy of these treatments is unknown, trials to evaluate ZMapp, TKM-Ebola, and convalescent plasma are currently under way in Sierra Leone and Guinea.

Ribavirin has not shown anti-*Ebolavirus* activity in vitro and does not protect *Ebolavirus*-infected primates. Other agents that have been studied for the treatment or prevention of EVD include nucleoside analog inhibitors of S-adenosylhomocysteine hydrolase, interferon beta, horse- or goat-derived immune globulins, human-derived convalescent immune globulin preparations, recombinant human interferon alpha-2, recombinant human monoclonal antibody against the envelope glycoprotein (GP) of Ebola virus, DNA vaccines expressing either envelope GP or nucleocapsid protein genes of Ebola virus, protein C, and recombinant inhibitor of factor VIIa/tissue factor.

Public Health Measures

Historically, the cornerstone of control in low-resource regions has been isolation of the ill. While this strategy, in and of itself, may have been effective in small rural outbreaks, it has little to offer to infected people and their families.

Because Ebola is transmitted by contact with bodily fluids of symptomatic patients, transmission can be interrupted by a combination of early diagnosis, contact tracing, patient

isolation, infection control, and safe burial practices. As has been demonstrated in the West African outbreak, however, the quality of clinical management of EVD patients while in treatment units, active communication with family members, and increased numbers of discharged patients plays a critical role in the success of efforts that target interrupting outbreak transmission. In effect, if the community is not convinced that an Ebola treatment unit is providing quality care, they are likely to avoid that treatment unit, which results in infectious patients remaining longer in the community.

When clinicians encounter patients with a history of exposure to Ebola and symptoms that are potentially consistent with EVD, they should first notify local public health authorities. In the United States, this would be county public health departments.

The CDC has designated US hospitals into three categories: those without special capacity to care for patients with suspected or proven EVD, those where patients with suspected EVD can be safely assessed and cared for while the infection is ruled out (usually within 72 hours), and those where comprehensive care of confirmed EVD patients can be safely provided. Every front-line healthcare worker should be confident that he or she can safely move patients with suspected EVD to the next higher level of care. Regardless of the level of care of a particular center, only trained employees should be permitted to care for these patients. Personal protective measures include diligent, rigorous, observed use of contact precautions via full barrier protection and flawless hand hygiene after care duties. These patients can produce prodigious volumes of infectious diarrhea and other body fluids, which must be handled with utmost care.

Given the relative immunosuppression of pregnancy, and epidemiologic data suggesting that pregnant women have a more severe than usual course when they become infected with Ebola, it is recommended that pregnant women not care for patients with Ebola.

The CDC recommends that women with Ebola and female survivors of Ebola not nurse their infants. Also, male survivors of EVD are recommended to either abstain from sexual activity or use condoms after recovery. The duration of these measures has not yet been delineated.

Vaccines

During the West Africa Ebola outbreak, at least two vaccines for Ebola have been under investigation in clinical trials. One (NIAID/ GSK Ebola vaccine) is a recombinant chimpanzee cold virus used as a vector to deliver segments of genetic material from Zaire Ebola virus (cAd3-ZEBOV). The other (VSV-EBOV Merck vaccine) is a genetically engineered version of vesicular stomatitis virus (VSV) in which the outer protein is replaced with a gene segment from the outer protein of Zaire Ebola virus. In March 2015, preliminary results from a phase II trial involving more than 600 participants in Liberia showed that both cAd3-ZEBOV and VSV-EBOV were safe. In addition, between October 2014 and June 2015, 120 Swiss adult participants receiving either high-dose cAd3-ZEBOV, low-dose cAd3-ZEBOV, or placebo were enrolled in a phase 1/2a randomized, double-blind, placebo-controlled trial which demonstrated that the vaccine was well tolerated and could elicit a robust immune response lasting 6 months after vaccination. Between April and July 2015, a phase III cluster-randomized trial utilizing a ring vaccination strategy to test safety and efficacy of VSV-EBOV in contacts of newly infected EVD cases took place in southwestern Guinea: when a new case was identified, close contacts were randomized to receive VSV-EBOV either immediately or 3 weeks later. Interim analyses suggested a significantly lower incidence of EVD in participants who received early VSV-EBOV vaccination compared to participants who received delayed vaccination, and randomization was discontinued so that all participants could receive this vaccine immediately. No one who received the vaccine has yet developed clinical EVD beyond a defined incubation period. While guidelines for widespread deployment of the vaccine have not been established, under investigational protocols, VSV-EBOV has been administered for post-exposure prophylaxis in some repatriated patients who were exposed to Ebola virus while caring for EVD patients in West Africa. In addition, since October 2015, VSV-EBOV vaccination has been administered to

contacts from the UK and Sierra Leone who had been exposed to EVD survivors with recrudescent infection; no secondary infections have been reported in these vaccinated contacts.

FURTHER READING

Bausch, D.G., 2011. Viral hemorrhagic fevers. In: Goldman's Cecil Medicine, twenty-fourth ed. Saunders Elsevier, Philadelphia, pp. 2147–2155.

CDC, 2014. Clinical Inquiries Regarding Ebola Virus Disease Received by CDC—United States, July 9–November 15, 2014. MMWR 63 (Early Release), 1–5.

CDC, 2014. Interim U.S. Guidance for Monitoring and Movement of Persons with Potential Ebola Virus Exposure. Updated December 24. Available at <http://www.cdc.gov/vhf/ebola/exposure/monitoring-and-movement-of-persons-with-exposure.html> (accessed February 16, 2015).

CDC, 2014. Support Services for Survivors of Ebola Virus Disease—Sierra Leone, 2014. MMWR 63 (50), 1205–1206.

CDC, 2015. Ebola (Ebola Virus Disease)—Diagnosis. Available at <http://www.cdc.gov/vhf/ebola/diagnosis/> (accessed February 20, 2015).

CDC, 2015. 2014 Ebola Outbreak in West Africa—Case Counts. Available at <http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html>.

CDC, 2016. CDC Health Information for International Travel. Oxford University Press, New York.

Chertow, D.S., Kleine, C.K., Edwards, J.K., et al., 2014. Ebola virus disease in West Africa—clinical manifestations and management. N. Engl. J. Med. 371, 2054–2057.

Epstein, H., 2014. Ebola in Liberia: an epidemic of rumors. New York Review of Books, 91–95.

Henao-Restrepo, A.M., Longini, I.M., Egger, M., et al., 2015. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet 386 (9996), 857–866. Online, July 31.

International Committee on Taxonomy of Viruses. Available at <http://ictvonline.org/virusTaxonomy.asp?version=2012> (accessed February 16, 2015).

Ippolito, G, et al., 2012. Viral hemorrhagic fevers: advancing the level of treatment. BMC Med. 10, 31.

King, J.W., Ebola virus infection. *Medscape*. Available at <http://emedicine.medscape.com/article/216288-overview> (accessed February 16, 2015).

Kortepeter, M.G., Bausch, D.G., Bray, M., 2011. Basic clinical and laboratory features of filoviral hemorrhagic fever. J. Infect. Dis. 204 (Suppl. 3), S810–S816. doi:10.1093/infdis/jir299.

Knust, B., Rollin, P.E., Infectious Diseases Related to Travel: Viral hemorrhagic fevers. CDC 2016 "Yellow Book" Chapter 3. Available at <http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/viral-hemorrhagic-fevers>.

Lyon, G.M., et al., 2014. Clinical care of two patients with Ebola virus disease in the United States. N. Engl. J. Med. 371, 2402–2409.

Meltzer, E., 2012. Arboviruses and viral hemorrhagic fevers (VHF). Infect. Dis. Clin. N. Am. 26, 479–496.

Prescott, J., et al., 2015. Post-mortem stability of Ebola virus. Emerg. Infect. Dis. doi:10.3201/eid2105.150041. Available at <http://wwwnc.cdc.gov/eid/article/21/5/15-0041_article>.

Towner, J.S., Rollin, P.E., Bausch, D.G., et al., 2004. Rapid diagnosis of Ebola hemorrhagic fever by reverse transcription-PCR in an outbreak setting and assessment of patient viral load as a predictor of outcome. J. Virol. 78 (8), 4330–4341.

West, T.E., von Saint André-von Arnim, A., 2014. Clinical presentation and management of severe Ebola virus disease. Ann. Am. Thorac. Soc. 11 (9), 1341–1350.

WHO, 2015. WHO Fact Sheet: Ebola Virus Disease. Available at <http://www.who.int/mediacentre/factsheets/fs103/en/> (accessed December 11, 2014).

WHO Ebola Response Team, 2014. Ebola Disease in West Africa—The First 9 Months of the Epidemic and Forward Projections. N. Engl. J. Med. 371, 1481–1495.