

# Early Release From Red Book<sup>®</sup>

## ..... 2015 REPORT OF THE COMMITTEE ON INFECTIOUS DISEASES

### **Hemorrhagic Fevers Caused by Filoviruses: Ebola and Marburg**

**CLINICAL MANIFESTATIONS:** Data on Ebola and Marburg virus infections primarily are derived from adult populations. More is known about Ebola virus disease than Marburg virus disease, although the same principles apply generally to all filoviruses that cause human disease. Asymptomatic cases of human filovirus infections have been reported, and symptomatic disease ranges from mild to severe disease; case fatality rates for severely affected people range from 25% to 90% (approximately 70% in the 2014 outbreak). After a typical incubation period of 8 to 10 days (range, 2–21 days), disease in children and adults begins with nonspecific signs and symptoms including fever, headache, myalgia, abdominal pain, and weakness followed several days later by vomiting, diarrhea, and unexplained bleeding or bruising. Respiratory symptoms are more common in children, and central nervous system manifestations are less common in children than in adults. A fleeting maculopapular rash on the torso or face after approximately 4 to 5 days of illness may occur. Conjunctival injection or subconjunctival hemorrhage may be present. Hepatic dysfunction, with elevations in aspartate transaminase (AST) markedly higher than alanine transaminase (ALT), and metabolic derangements, including hypokalemia, hyponatremia, hypocalcemia, and hypomagnesemia, are common. In the most severe cases, microvascular instability ensues around the end of the first week of disease. Although hemostasis is impaired, hemorrhagic manifestations develop in a minority of patients. In the 2001 Uganda Sudan Ebola virus outbreak, all children with laboratory-confirmed Ebola virus disease were febrile, and only 16% had hemorrhage. The most common hemorrhagic manifestations consist of bleeding from the gastrointestinal tract, sometimes with oozing from the mucus membranes or venipuncture sites in the late stages. Central nervous system manifestations and renal failure are frequent in end-stage disease. In fatal cases, death typically occurs around 10 to 12 days after symptom onset, usually resulting from viral- or bacterial-induced septic shock and multi-organ system failure. Approximately 30% of pregnant women with Ebola virus disease present with spontaneous abortion and vaginal bleeding. Maternal mortality approaches 90% when infection occurs during the third trimester. All neonates born to mothers with active Ebola virus disease to date have died. The exact cause of the neonatal deaths is unknown.

**ETIOLOGY:** The Filoviridae (from the Latin *filo* meaning thread, referring to their filamentous shape) are single-stranded, negative-sense RNA viruses. Four of the 5 species of virus in the Ebolavirus genus and both of the known species of virus in the Marburgvirus genus are associated with human disease. All of the known human pathogenic filoviruses are endemic only in sub-Saharan Africa.

**EPIDEMIOLOGY:** Fruit bats are believed to be the animal reservoir for Ebolaviruses. Human infection is believed to occur from inadvertent exposure to infected bat excreta or saliva following entry into roosting areas in caves, mines, and forests. Nonhuman primates, especially gorillas and chimpanzees, and other wild animals also may become infected from bat contact and serve as intermediate hosts that transmit filoviruses to humans through contact with their blood and bodily fluids, usually associated with hunting and butchering (see Control Measures, Environmental). For unclear reasons, filovirus outbreaks tend to occur after prolonged dry seasons.

Molecular epidemiologic evidence shows that most outbreaks result from a single point introduction (or very few) into humans from wild animals, followed by human-to-human transmission, almost invariably fueled by health care-associated transmission in areas with inadequate infection control equipment and resources. Although filoviruses are the most transmissible of all hemorrhagic fever viruses, secondary attack rates in households still generally are only 15% to 20% in African communities, and are lower if proper universal and contact precautions are maintained. Human-to-human transmission usually occurs through oral, mucous membrane, or nonintact skin exposure to bodily fluids of a symptomatic person with filovirus disease, most often in the context of providing care to a sick family or community member (community transmission) or patient (health care-associated transmission). Funeral rituals that entail the touching of the corpse also have been implicated, as has transmission through breastfeeding from infected mothers (see Control Measures, Breastfeeding). Infection through fomites cannot be excluded. Health care-associated transmission is highly unlikely if rigorous infection control practices are in place in health care facilities (see Isolation of the Hospitalized Patient). Ebola is not spread through the air, by water, or in general by food (with the exception of bush meat; see Control Measures, Environmental). Respiratory spread of virus does not occur.

Children may be less likely to become infected from intrafamilial spread than adults when a primary case occurs in a household, possibly secondary to the fact that they are not typically primary caregivers of sick individuals and are less likely to take part in funeral rituals that involve touching and washing of the deceased person's body. Underreporting of Ebola cases in children also is possible. In 2 outbreaks in which large numbers of children were affected, school-aged children and adolescents had increased survival rates compared with children younger than 5 years and adults.

The degree of viremia appears to correlate with the clinical state. People are most infectious late in the course of severe disease, especially when copious vomiting, diarrhea, and/or bleeding are present. Transmission during the incubation period, when the person is asymptomatic, is not believed to occur. Virus may persist in a few immunologically protected sites for several weeks after clinical recovery, including in testicles/semen, human milk, and the chambers of the eye (resulting in transient uveitis and other ocular problems). Because of the risk of sexual transmission, abstinence or use of condoms is recommended for 3 months after recovery.

The 2014 West Africa Ebola outbreak is the largest since the virus was first identified in 1976 and the first in that region of the continent. A simultaneous outbreak of Ebola occurred in the Democratic Republic of the Congo (formerly Zaire), but this outbreak was caused by a different species than the species causing the outbreak in West Africa. Updated information on identification and current management of people traveling from areas of transmission or with contact with a person with Ebola virus infection can be

found on the Centers for Disease Control and Prevention (CDC) Web site ([www.cdc.gov/vhf/ebola/](http://www.cdc.gov/vhf/ebola/)) and the AAP Web site (for pediatricians: [www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Children-and-Disasters/Pages/Ebola.aspx](http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Children-and-Disasters/Pages/Ebola.aspx) and for parents or caregivers: [www.healthychildren.org/English/health-issues/conditions/infections/Pages/Ebola.aspx](http://www.healthychildren.org/English/health-issues/conditions/infections/Pages/Ebola.aspx)).

**DIAGNOSTIC TESTS:** The diagnosis of Ebola virus infection should be considered in a person who develops a fever within 21 days of travel to an endemic area (particularly Sierra Leone, Liberia, and Guinea in the 2014 outbreak). Because initial clinical manifestations are difficult to distinguish from those of more common febrile diseases, prompt laboratory testing is imperative in a suspected case. Filovirus disease can be diagnosed by testing of blood by reverse transcriptase-polymerase chain reaction (RT-PCR) assay, enzyme-linked immunosorbent assay (ELISA) for viral antigens or immunoglobulin (Ig) M, and cell culture, with the latter being attempted only under biosafety level-4 conditions. Viral RNA generally is detectable by RT-PCR assay within 3 to 10 days after the onset of symptoms. Postmortem diagnosis can be made via immunohistochemistry testing of skin, liver, or spleen. Testing generally is not performed in routine clinical laboratories. Local or state public health department officials must be contacted and can facilitate testing at a regional certified laboratory or at the CDC.

Malaria, measles, typhoid fever, Lassa fever, and dengue should be included in the differential diagnosis of a symptomatic person returning from Africa within 21 days.

**TREATMENT:** People suspected of having Ebola or Marburg virus infection immediately should be placed in isolation and public health officials should be notified. Management of patients with filovirus disease primarily is supportive, including oral or intravenous fluids with electrolyte repletion, vasopressors, blood products, total parenteral nutrition, and antimalarial and antibiotic medications when coinfections are suspected or confirmed ([www.cdc.gov/vhf/ebola/treatment/index.html](http://www.cdc.gov/vhf/ebola/treatment/index.html)). Volume losses can be enormous (10 L/day in adults), and some centers report better results with repletion using lactated Ringer solution rather than normal saline solution in management of adult patients in the United States. When antibiotic agents are used to treat sepsis, the medications should have coverage for intestinal microbiota based on limited evidence of translocation of gut bacteria into the blood of patients with filovirus disease. Nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and intramuscular injections should be avoided because of the risk of bleeding.

There currently are no specific therapies approved by the US Food and Drug Administration (FDA) for filovirus infection, although a number of experimental approaches show promise in animal models. Expanded-access programs for monoclonal antibodies, small inhibitory RNAs, antisense compounds, nucleoside analogues, and convalescent plasma have been employed on a limited scale to date in humans; the effect of these therapies on the course of human disease is unclear. Although active in other hemorrhagic fever virus infections, ribavirin has no efficacy against filoviruses and should not be used. Corticosteroids should not be administered except for replacement in suspected or confirmed adrenal insufficiency or refractory septic shock.

**ISOLATION OF THE HOSPITALIZED PATIENT:** Standard, contact, and droplet precautions are recommended for management of hospitalized patients with known or suspected Ebola virus disease. Although not required, it may be prudent to place the patient in a negative-pressure room when available, despite the lack of evidence for natural aerosol

transmission between humans, because of the large amount of fluid losses and copious vomiting that may lead to temporary aerosolization of the virus. Access to the patient should be limited to a small number of designated staff and family members with specific instructions and training on filovirus infection control and on the use of personal protective equipment. Although experience suggests that standard universal and contact protections usually are protective, viral hemorrhagic fever precautions consisting of at least 2 pairs of gloves, fit-tested N95 or particulate respirator, impermeable or fluid-resistant gown, face shield, protective apron, and shoe covers or rubber boots are recommended when filovirus infection is confirmed or suspected. No skin should be showing, and a buddy system should be employed for donning and doffing the personal protective equipment. All health care workers should be knowledgeable with and proficient in the donning and doffing of personnel protective equipment prior to participating in management of a patient. Particulate respirators are recommended when aerosol-generating procedures, such as endotracheal intubation, are performed. Current guidance from the CDC on personal protective equipment can be found on the CDC Web site ([www.cdc.gov/vhf/ebola/hcp/index.html](http://www.cdc.gov/vhf/ebola/hcp/index.html)).

## **CONTROL MEASURES**

**Contact Tracing.** Monitoring and movement of people with potential Ebola virus exposure currently is based on the degree of possible risk. Categories include high risk, some risk, low risk, and no identifiable risk. Full descriptions of recommended management for people in these categories can be found on the CDC Web site ([www.cdc.gov/vhf/ebola/exposure/monitoring-and-movement-of-persons-with-exposure.html](http://www.cdc.gov/vhf/ebola/exposure/monitoring-and-movement-of-persons-with-exposure.html)).

Asymptomatic people at high, some, or low risk should have active monitoring consisting of, at a minimum, daily reporting of measured temperatures and symptoms consistent with Ebola (including severe headache, fatigue, muscle pain, weakness, diarrhea, vomiting, abdominal pain, or unexplained hemorrhage) by the individual to the public health authority. People being actively monitored should measure their temperature twice daily, monitor themselves for symptoms, report as directed to the public health authority, and immediately notify the public health authority if they develop fever or other symptoms. Restrictions on movement apply to asymptomatic people in the high-risk category and may be considered by public health authorities for asymptomatic people with some risk as well. Restrictions on movement are not recommended for asymptomatic people with low or no identifiable risk. Despite lack of evidence for transmission during the incubation period, it usually is recommended that exposed people avoid close contact or activities with household members that might result in exposure to bodily fluids, such as sharing of utensils, kissing, and sexual intercourse. Hospitalization of asymptomatic contacts is not warranted, but people who develop fever or other manifestations of filovirus disease should be isolated immediately until the diagnosis can be ruled out.

**Immunoprophylaxis.** Although there are currently no FDA-approved vaccines, a number of experimental vaccines and other compounds have been shown to be efficacious in nonhuman primate models, including when given as postexposure prophylaxis. Several Ebola virus vaccine candidates are presently in Phase I trials in humans.

**Breastfeeding.** Although Ebola virus has been detected in human milk, it is not known whether Ebola virus can be transmitted from mothers to their infants through breastfeeding. However, given what is known about transmission of Ebola virus, regardless of breastfeeding status, infants whose mothers are infected with Ebola virus already are at high risk of acquiring Ebola virus infection through close contact with the mother and

are at high risk of death overall. Therefore, when safe replacements to breastfeeding and infant care exist, mothers with probable or confirmed Ebola virus infection should not have close contact with their infants (including breastfeeding). In resource-limited settings, however, because nonbreastfed infants are at increased risk of death from starvation and other infectious diseases, such as diarrheal and respiratory diseases, these risks must be carefully weighed against the risk of Ebola virus infection. There is not enough evidence to provide guidance on when it is safe to resume breastfeeding after a mother's recovery, unless her milk can be demonstrated to be Ebola virus-free by laboratory testing. In the 1 case in which human milk was tested, Ebola virus was identified in the milk of a lactating woman 7 and 15 days after disease onset.

**Travelers.** Nonessential travel to areas affected by the 2014 Ebola outbreak is not recommended. Travelers to an area affected by an Ebola outbreak should practice careful hygiene (eg, wash hands with soap and water or a 9:1 water to bleach solution, use an alcohol-based hand sanitizer; avoid contact with blood and body fluids). Travelers should not handle items that may have come in contact with an infected person's blood or body fluids, such as clothes, bedding, needles, and medical equipment. Funeral or burial rituals that require handling the body of someone who has died from Ebola should be avoided. Given the current countries affected by the 2014 Ebola outbreak, travelers should avoid hospitals where Ebola patients are being treated in areas of Africa with endemic disease; the United States embassy or consulate often is able to provide advice on facilities that should be avoided. Following return to the United States, travelers should monitor their health closely for 21 days and seek medical care immediately if they develop symptoms of Ebola (see Control Measures, Environmental). State laws mandating confinement or quarantine may apply. Current travel information for countries affected by Ebola can be found on the CDC Web site ([www.cdc.gov/vhf/ebola/travelers/index.html](http://www.cdc.gov/vhf/ebola/travelers/index.html)).

**Environmental.** Avoiding contact with bats, primarily by avoiding entry into caves and mines in areas with endemic disease, is a key prevention measure for filoviruses. People also should avoid exposure to fresh blood, bodily fluids, or meat of wild animals, especially nonhuman primates but also bats, porcupines, duikers (a type of antelope), and other mammals, in areas with endemic filovirus disease.

**Public Health Reporting.** Because of the risk of health care-associated transmission, state/local health departments and the CDC should be contacted for specific advice about confirmation and management of suspected cases. In the United States, Ebola and Marburg hemorrhagic fevers are reportable by guidelines of the Council of State and Territorial Epidemiologists. If a filoviral hemorrhagic fever is suspected, the state/local health department or CDC Emergency Operations Center (770-488-7100) should be contacted to assist with case investigation, diagnosis, management, and control measures.

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*The recommendations in this publication do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.*

*The information in this chapter is considered an early release from the 2015 Red Book (in press). Information may be updated closer to publication. Web site addresses are as current as possible but may change at any time.*