Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

166 Marburg and Ebola Hemorrhagic Fevers (Filoviruses)

Thomas W. Geisbert

SHORT VIEW SUMMARY

Definition
- Marburg hemorrhagic fever and Ebola hemorrhagic fever are severe and often fatal diseases characterized by fever, headache, malaise, myalgia, coagulation disorders, and multiorgan failure.

Epidemiology
- Human outbreaks occur sporadically in regions of Central Africa.
- Recent evidence suggests that bats may play a role as a reservoir host.
- The manner in which filovirus outbreaks are initiated is unknown; however, it is thought that the initial cases occur as a result of contact with an infected animal.
- Nosocomial transmission has occurred frequently during outbreaks of filovirus hemorrhagic fever in endemic areas.

Diagnosis
- Clinical symptoms are nonspecific, but a constellation of symptoms, including fever, headache, malaise, myalgia, sore throat, vomiting, and, in particular, the appearance of a maculopapular rash may indicate infection with a filovirus.
- Antigen-capture enzyme-linked immunosorbent assay and polymerase chain reaction are the most frequently used assays to diagnose filovirus infection.

Treatment
- There are no approved postexposure treatments for filovirus infections.
- Treating patients infected with Marburg or Ebola viruses consists primarily of intensive supportive care that is directed toward maintaining effective blood volume and electrolyte balance.
- Several experimental treatments have shown promise in nonhuman primate models of filovirus infection, including vesicular stomatitis virus–based postexposure vaccines, small interfering RNAs, antisense oligonucleotides, and pools of monoclonal antibodies.

Prevention
- There are no approved vaccines against Marburg or Ebola viruses.
- Barrier nursing procedures include wearing protective clothing, masks, and eye shields.
- Isolation of infected patients and close contacts is essential.
- Avoid contact with bush meat and sick animals, particularly nonhuman primates, in endemic regions.

Viral hemorrhagic fever (VHF) is a syndrome characterized by fever, malaise, myalgia, and blood coagulation disorders that can progress to multiorgan failure, shock, and death in many cases. VHF is caused by members of four different families of RNA viruses. Among the VHF members of the family Filoviridae, Marburg virus (MARV) and Ebola virus (EBOV) are the most feared because of their dramatic clinical presentation, unusually high case-fatality rates of up to 90%, and because their natural history remains a mystery. In addition to concerns of natural outbreaks in regions of Central Africa, EBOV and MARV are known to have been the subjects of former biological weapons programs and have the potential for deliberate misuse (see Chapter 15).[1,2] Currently, there are no filovirus vaccines or treatments approved for human use. For these reasons, EBOV and MARV have recently been included as only 2 of 11 human pathogens and only 2 of 4 viruses on the new United States Department of Health and Human Services Tier 1 list of Category A select agents (the other two viruses are variola major and minor).[3] In addition to causing significant disease in humans, filoviruses have decimated populations of great apes in the Congo basin, further impacting an already endangered species.

VIRUS CHARACTERIZATION

The family Filoviridae is divided into two genera: MARV and EBOV. Although the MARV genus contains a single species, the EBOV genus consists of five distinct species: *Bundibugyo ebolavirus (BEBOV), Côte d'Ivoire ebolavirus (CIEBOV; also known as Ivory Coast ebolavirus), Reston ebolavirus (REBOV), Sudan ebolavirus (SEBOV), and Zaire ebolavirus (ZEBOV).*[4] Nucleotide and amino-acid differences between MARV and EBOV are each approximately 55%, and there is no serologic cross-reactivity between these viruses. In comparison, EBOV species show 37% to 41% differences in nucleotide and amino-acid sequences, and there are varying degrees of cross-reactivity among the EBOV species.

Filoviruses are enveloped, nonsegmented, negative-strand RNA viruses. Filovirus particles take on a variety of forms, from circular or "6"-shaped to prototypical straight filaments, for which the virus family is named (Fig. 166-1). Although the length of the virions is variable, MARV particles average close to 800 nm, and EBOV virions measure about 1 μM. The diameter of all filovirus particles uniformly measures about 80 nm.[5] Filovirus particles contain an approximately 19-kb noninfectious genome that encodes seven structural proteins, with a gene order of 3′ leader, nucleoprotein (NP), virion protein 35 (VP35), VP40, glycoprotein (GP), VP30, VP24, RNA-dependent RNA polymerase L protein, and 5′ trailer. Four of these proteins are associated with the viral genomic RNA in the ribonucleoprotein complex: NP, VP30, VP35, and the L protein. Some proteins of the ribonucleoprotein complex have additional functions. For example, VP35 has been shown to act as an interferon antagonist.[6] VP40 serves as the matrix protein and mediates particle formation, and in the case of MARV, it has also been shown to interfere with host innate immune responses.[7] VP24 is another structural protein associated with the membrane and also interferes with interferon signaling for EBOV.[8]

The GP is the surface glycoprotein that forms the spikes on the virion and is the effector for receptor binding and membrane fusion. An important distinction of EBOV from MARV is that the MARV GP is encoded in a *single open reading frame* (ORF), whereas the EBOV GP is encoded in *two ORFs*.[9,10] The single MARV ORF translates into the structural surface GP. In contrast, the two EBOV ORFs are linked together by slippage of the L polymerase at an editing site (a string of seven consecutive template uracil residues) to insert an eighth uracil. This process results in the production of a messenger RNA (mRNA)

KEYWORDS

Ebola virus; Filoviridae; filovirus; Marburg virus; viral hemorrhagic fever

transcript that permits read-through translation of full-length GP. However, only about 20% of the mRNA transcripts are edited and translated into structural surface GP. The remaining 80% of unedited mRNA transcripts result in the production of a truncated soluble GP (sGP) that is secreted in large quantities from infected cells. Although the function of sGP has not been fully elucidated, it has been postulated that sGP subverts the host immune response by both passively absorbing antibodies directed at the full-length structural GP[11,12] and by triggering the proliferation of B cells that preferentially bind sGP.[13]

EPIDEMIOLOGY

Marburg Hemorrhagic Fever

The first documented outbreak of VHF caused by a filovirus occurred in 1967 when there were three concurrent episodes of lethal MARV infections in Marburg and Frankfurt, Germany and in Belgrade (in the former Yugoslavia) among laboratory workers exposed to blood and tissue products of African green monkeys imported from Uganda (Fig. 166-2).[14] Secondary transmission to medical staff and family members was also documented. In total, 31 patients became infected, and 7 of these patients died. During the next 2 decades, MARV was associated with sporadic, isolated, usually fatal cases among residents and travelers in southeast Africa.

In 1998 to 2000, there was a prolonged outbreak involving 154 cases of MARV hemorrhagic fever (HF) in Durba, Democratic Republic of the Congo (DRC) that was associated with individuals working in an underground gold mine.[15] Case-fatality rates from this outbreak are unclear but may be up to 83%. This outbreak was unique and complicated by the fact that it had multiple introductions of MARVs of different phylogenetic lineages and included strains that are thought to be more pathogenic (Angola)[16,17] than others. The largest and most lethal MARV outbreak to date occurred in 2004 to 2005 in northern Angola.[16] This outbreak involved 252 cases, with a case-fatality rate of 90%. The epidemic was driven largely by nosocomial transmission; however, community-acquired infection was documented toward the end of the outbreak. Between 2007 and 2012, several small episodes of MARV HF were reported in Uganda, with one case being exported to the United States[18] and one to the Netherlands.[19]

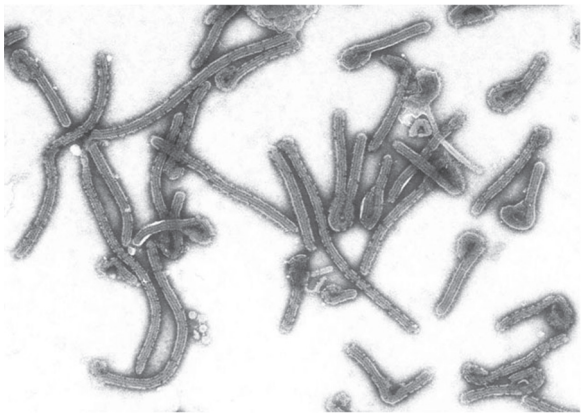

FIGURE 166-1 Electron micrograph of Sudan ebolavirus virions. Negatively contrasted filovirus particles obtained from culture fluids from infected Vero cells (magnification, ×12,000).

Ebola Hemorrhagic Fever

EBOV was first recognized during near-simultaneous explosive outbreaks in 1976 in small communities in the former Zaire (now the DRC) and Sudan (see Fig. 166-2).[20,21] There was significant secondary transmission through the reuse of unsterilized needles and syringes and nosocomial contacts. These independent outbreaks involved serologically distinct species, ZEBOV and SEBOV. The ZEBOV outbreak consisted of 318 cases and 280 deaths (88% mortality), whereas the SEBOV outbreak involved 284 cases with 151 deaths (53% mortality). Since 1976, ZEBOV has appeared sporadically in Central Africa, causing several small- to midsize outbreaks between 1976 and 1979. In 1995, there was a large epidemic of ZEBOV HF involving 315 cases, with an 81% case-fatality rate, in Kikwit, a community in the DRC.[22]

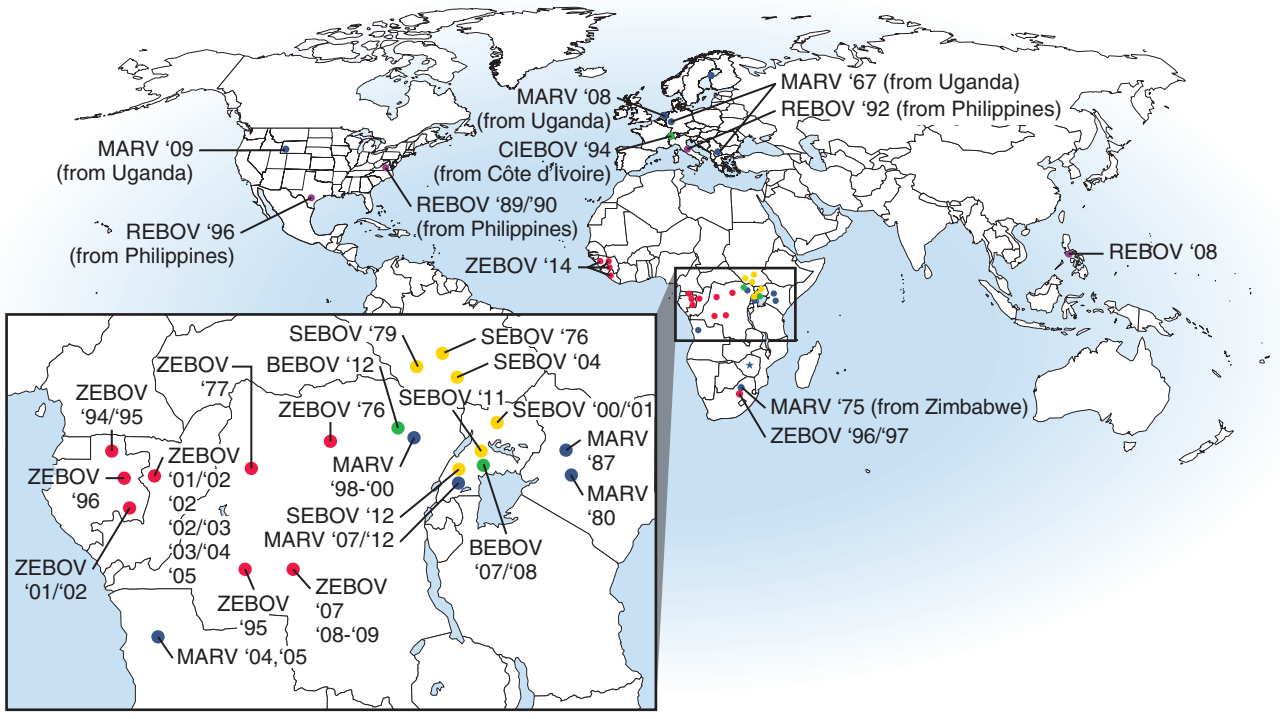

FIGURE 166-2 Locations of filovirus infections and outbreaks. BEBOV, Bundibugyo ebolavirus; CIEBOV, Côte d'Ivoire ebolavirus, MARV, Marburg virus; REBOV, Reston ebolavirus; SEBOV, Sudan ebolavirus; ZEBOV, Zaire ebolavirus. *(From European Centre for Disease Prevention and Control. Epidemiological Update: Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Available at http://www.ecdc.europa.eu/en/press/news/_layouts/forms/News_DispForm.aspx?List=8db7286c-fe2d-476c-9133-18ff4cb1b568&ID=998. Accessed May 12, 2014.)*

Meanwhile, between 1994 and 1997, there were smaller outbreaks caused by ZEBOV in Gabon. Since 2000, there have been near-yearly occurrences of ZEBOV in Gabon, DRC, or the Republic of Congo. During 2014, ZEBOV outbreaks were reported for the first time in West Africa in the countries of Guinea, Liberia, and Sierra Leone. The Central Africa outbreaks of ZEBOV have also involved a catastrophic decline in populations of great apes.[23,24] The largest EBOV outbreak on record involved 425 cases, with a 53% case-fatality rate.[25] This outbreak occurred in 2000 to 2001 in Sudan and was caused by SEBOV. Smaller outbreaks of SEBOV have occurred in Sudan in 2004 and in Uganda in 2011 and 2012.

In 1989 to 1990, a third species of EBOV, REBOV, appeared in Reston, Virginia in association with an outbreak of VHF among cynomolgus macaques imported to the United States from the Philippine Islands.[26] Hundreds of monkeys were infected (with high mortality) in this outbreak, but no human cases occurred. Four animal caretakers seroconverted to REBOV with no overt disease. Epizootics in cynomolgus monkeys recurred at other facilities in Europe and the United States through 1992 and again in 1996. Subsequently, REBOV has been found in the Philippines on several occasions, with surprising reports documenting infections in domestic pigs.[27]

A fourth species of EBOV, CIEBOV, was identified in Côte d'Ivoire in 1994.[28] The virus was isolated from an ethnologist who had worked in the Tai Forest reserve and became infected after a necropsy on a chimpanzee. The individual became ill with symptoms consistent with filovirus infection and survived infection. The chimpanzee originated from a troop that lost several members to an illness that was subsequently identified as being caused by CIEBOV.

The latest and fifth species of EBOV, BEBOV, was discovered in Uganda late in 2007 during an outbreak that involved 56 confirmed cases and an approximate 40% case-fatality rate.[29] A more recent outbreak of BEBOV occurred late in 2012 in the DRC and involved 52 probable cases and a 48% case-fatality rate.[30]

NATURAL HISTORY

Human and nonhuman primates are susceptible to filovirus infection and are considered to be end hosts rather than potential reservoirs. Surveys to identify animal reservoirs and arthropod vectors have been aggressively undertaken in endemic areas, particularly after most large filovirus outbreaks. Until recently, these efforts have been unsuccessful. Ecologic studies in 2003 to 2006 in Gabon and the Republic of Congo demonstrated the initial evidence for the presence of ZEBOV in three different species of fruit bats.[31] These studies showed the presence of viral RNA and antibodies, although the investigators were unable to isolate infectious ZEBOV. Subsequent studies in 2007, detecting MARV RNA and isolating infectious MARV from cave-dwelling fruit bats in Uganda, further support the view that bats may serve as a reservoir for filoviruses.[32] More recently, antibodies against REBOV were detected in fruit bats in the Philippines.[33] Although current data suggests a role for bats in maintaining filoviruses in nature, it remains unclear whether bats serve as the primary reservoir or whether other species are involved.

CLINICAL MANIFESTIONS AND DIAGNOSIS

Clinical and laboratory features of MARV and EBOV infection are nonspecific and include an incubation period of 2 to 21 days (mean, 4 to 10 days) with a sudden onset of fever, malaise and/or myalgia, and may include a variety of other nonspecific symptoms.[4,34] The presence of an erythematous, maculopapular rash may be observed (Fig. 166-3). A constellation of other coagulation disorders may occur, including bleeding from venipuncture sites and the gastrointestinal tract (see Fig. 166-3). Clinical pathology findings include leukopenia and lymphocytopenia with increased levels of neutrophils, thrombocytopenia, and increased serum levels of the liver-associated enzymes aspartate aminotransferase and alanine aminotransferase. Prolonged blood coagulation times and increased circulating levels of D-dimers are also associated with filovirus infections.[35,36]

Confirmation of filovirus infection requires detection of virus in blood or other tissues or the demonstration of filovirus-specific antibody. Assays most frequently used to diagnose filovirus infections include immunofluorescent antibody tests, enzyme-linked immunosorbent assays for filovirus antigen and specific immunoglobulin M (IgM) and IgG antibodies, and reverse-transcriptase polymerase chain reaction assay.[25,37-40] Other assays that have been used to confirm filovirus infection include immunohistochemistry of skin and other tissues, virus culture, and electron microscopy.[37,41,42]

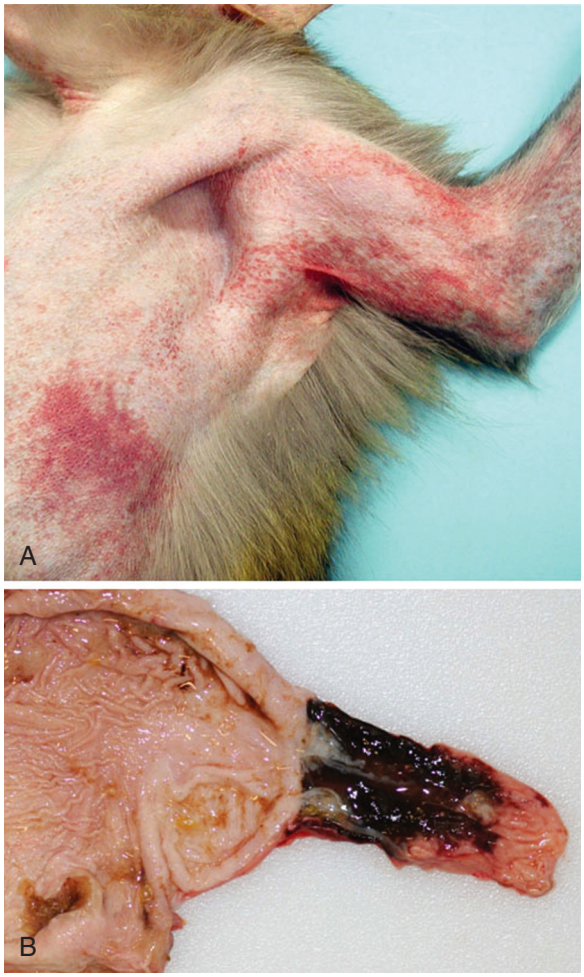

FIGURE 166-3 Representative gross necropsy lesions from nonhuman primates experimentally infected with filoviruses. A, Typical petechial rash of the left arm and chest of a rhesus macaque 11 days after infection with Marburg virus. **B,** Marked congestion of the duodenum at the gastroduodenal junction of a rhesus monkey 9 days after infection with Zaire ebolavirus.

PATHOGENESIS

Filoviruses are thought to enter the host through mucosal surfaces, small abrasions and/or tears in the skin, or by parenteral introduction. Both EBOV and MARV have a broad cell tropism, infecting a wide variety of cell types. Ultrastructural examination of tissues from fatal human cases and from experimentally infected nonhuman primates show that monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes, adrenal cortical cells, and several types of epithelial cells all lend support to replication of these viruses.[43-49] Systematic studies in nonhuman primates experimentally infected with MARV or ZEBOV suggest that monocytes, macrophages, and dendritic cells are the early and preferred replication sites.[47,48] Filovirus infection of mononuclear phagocytes appears to trigger a cascade of events involving the production and release of the procoagulant protein tissue factor,[35] as well as a variety of proinflammatory cytokines/chemokines and oxygen free radicals.[50,51] It is thought that the triggering of this chain of events is equally or, in fact, more critical to the development of the observed pathology than is any structural damage induced directly by the actual process of viral replication in host cells and/or tissues.

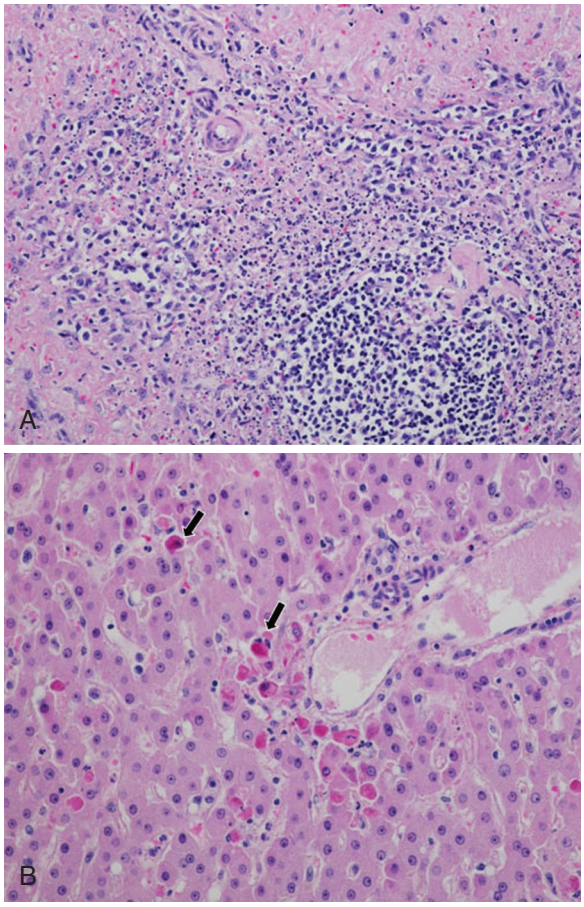

FIGURE 166-4 Histopathology of nonhuman primates experimentally infected with filoviruses. A, Necrosis and apoptosis of lymphocytes with concomitant lymphoid depletion in spleen of a rhesus monkey 9 days after infection with Zaire ebolavirus (hematoxylin and eosin stain; magnification, ×20). **B,** Councilman-like bodies *(arrows)* in the liver of a rhesus monkey 9 days after infection with Zaire ebolavirus (hematoxylin and eosin stain; magnification, ×20). *(**A** and **B** courtesy Karla Fenton, University of Texas Medical Branch–Galveston.)*

During filovirus infection, lymphoid depletion and necrosis are frequently observed in the spleen, thymus, and lymph nodes of patients with fatal disease and in nonhuman primates that are experimentally infected (Fig. 166-4). Although lymphoid tissues are primary sites of filovirus infection, there is usually little inflammatory cellular response in these or other infected tissues. Despite the large die-off and loss of lymphocytes during the disease course, the lymphocytes themselves do not support the production of progeny virus. Large numbers of lymphocytes undergo apoptosis in humans[52] and in experimentally infected nonhuman primates,[53] in part explaining the progressive lymphopenia and lymphoid depletion at death. Other morphologic lesions include focal necrosis in a number of organs, particularly the liver, where Councilman bodies are a prominent finding (see Fig. 166-4).

Coagulation disorders are a hallmark feature of filovirus infection, and results from many studies have shown biochemical and histologic evidence of disseminated intravascular coagulation in both humans and experimentally infected nonhuman primates.* The mechanism(s) responsible for triggering the coagulation disorders that typify filovirus infection are not completely understood. Results from several studies strongly suggest that expression or release of tissue factor from monocytes and macrophages infected with filoviruses plays a pivotal role in inducing the development of coagulation irregularities reported in filovirus HF.[35] However, coagulopathy noted during EBOV or MARV HF could be caused by several factors, especially during the later stages of disease.

*References 21, 35, 36, 45, 54, 55.

COUNTERMEASURES

Prevention

In the past, there has been little commercial interest for developing vaccines against filoviruses primarily because of the geographic location of epidemic areas and the small global market. However, the relatively recent classification of filoviruses as important biological defense pathogens, bolstered by the increased press coverage of the latest outbreaks in Central Africa, has dramatically changed perspectives regarding the need for vaccines against EBOV and MARV. Effective and fast-acting filovirus vaccines would be valuable for at-risk medical personnel, first responders, military staff and researchers, and also for targeted vaccination in the most affected populations (e.g., primarily health care workers and family members of confirmed or probable cases).

Although there are no approved vaccines or postexposure treatment modalities available for preventing or managing filovirus infections, there are at least seven different vaccine systems that have shown promise in completely protecting nonhuman primates against either EBOV or MARV HF, with five of these vaccines protecting animals against both EBOV and MARV.[56-58] Several of these vaccines require multiple injections to confer protective efficacy. However, in the setting of pathogens such as EBOV and MARV, which are indigenous to Africa and are also potential agents of bioterrorism, a single-injection vaccine is preferable. In the case of preventing natural infections, multiple-dose vaccines are both too costly and not practical (logistics and compliance) in developing countries. In the case of a deliberate release of these agents, there would be little time for deployment of a vaccine that requires multiple injections over an extended period of time. Thus, for most practical applications, a vaccine against the filoviruses necessitates a single immunization or, at the most, two injections within a very short time frame. Of the prospective filovirus vaccines, only two systems, one based on a replication-defective adenovirus serotype 5 and the other based on the recombinant vesicular stomatitis virus (VSV), have been shown to provide complete protection to nonhuman primates when administered as a single-injection vaccine.[59-61]

As noted above, the development of preventive filovirus vaccines that can confer complete protection in nonhuman primate models of filovirus infection has been encouraging. However, many challenges remain before any of these vaccines will be ready for human use or even phase I clinical trials. Among the most significant obstacles are the identification of a seemingly more pathogenic strain of MARV (strain Angola) in 2004 to 2005 and the identification of a new species of EBOV, BEBOV, in 2007. Filovirus vaccine development has primarily focused on two EBOV species, SEBOV and ZEBOV, and one MARV strain (strain Musoke). However, recent studies have shown that current vaccines do not completely protect nonhuman primates from disease and death after challenge with BEBOV.[62,63] In addition, few vaccines have been evaluated against the seemingly most pathogenic Angola strain of MARV, which has been associated with 90% case-fatality rates in humans and has been shown to have a faster disease course in macaques than other MARV strains.[16,17]

TREATMENT

At this time, treating patients infected with EBOV or MARV in endemic areas consists primarily of intensive supportive care that is directed toward maintaining effective blood volume and electrolyte balance. Several interventional therapies, including interferons, heparin, convalescent serum, and equine anti-ZEBOV IgG, have been used to treat natural and laboratory-acquired filovirus infections with little to no success.[55,64-66] This included a Russian laboratory exposure, where the patient was unsuccessfully treated shortly after exposure with a combination therapy that included anti-ZEBOV equine IgG, ribavirin, and reaferon.[65] A recent laboratory exposure to ZEBOV in Germany was treated with a recombinant VSV-based ZEBOV vaccine.[67] The individual survived with no evidence of overt clinical illness; however, whether the patient was actually exposed to ZEBOV or not remains uncertain. Ribavirin, which is used to treat several other VHFs, has no in vitro or in vivo effect on filoviruses.[68]

A number of postexposure treatments have shown promise in nonhuman primate models of filovirus infection. These include drugs that

modulate coagulopathy, including inhibitors of the tissue factor pathway that improved survival in a macaque model of ZEBOV HF,[69] as did drugs that treated protein C deficiency.[70] Recombinant VSV-based vaccines have shown good results in nonhuman primates when administered shortly after challenge, with results ranging from 50% protection for ZEBOV[71] to 100% protection for SEBOV[72] and MARV.[73,74] RNA-based treatments, including small interfering RNAs[75] and antisense oligonucleotides,[76] have also shown the ability to confer protection against death for ZEBOV and MARV when given shortly after challenge. There has been considerable controversy regarding the use of antibody-based treatments. Early studies using convalescent blood,[77] high-titer polyclonal equine IgG,[78] and a human recombinant monoclonal antibody[79] failed to show any beneficial effect against ZEBOV in nonhuman primates. However, more recent studies using purified polyclonal nonhuman primate IgG[80] and pools of recombinant monoclonal antibodies[81,82] have demonstrated the ability to protect macaques from lethal MARV and/or ZEBOV infection. There are several differences in these current studies, including the specific reagents used, regimen of treatment, and challenge viruses used. Of importance, it is known that the early studies used a wild-type ZEBOV isolate that consisted of a high population of viruses containing a series of 7 consecutive uracils (7Us) at the *GP* gene editing site, meaning that this isolate produces normal amounts of sGP. In contrast, it is known that at least two of the more recent studies used a variant ZEBOV that contained high populations with an additional uracil residue in the *GP* gene editing site,[83] meaning that at least in the early stages of replication, this virus did not produce as much sGP as wild-type ZEBOV. Future studies will need to more fully assess the potential of antibody-based therapies against the seemingly more pathogenic wild-type "7U" ZEBOV isolates.

Key References

The complete reference list is available online at Expert Consult.

2. Borio L, Inglesby T, Peters CJ, et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA*. 2002;287:2391-2405.
4. Feldmann H, Sanchez A, Geisbert TW. Filoviridae: Marburg and Ebola viruses. In: Knipe DM, Howley PM, eds. *Fields Virology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:923-956.
6. Basler CF, Wang X, Muhlberger E, et al. The Ebola virus VP35 protein functions as a type I IFN antagonist. *Proc Natl Acad Sci U S A*. 2000;97:12289-12294.
7. Valmas C, Grosch MN, Schumann M, et al. Marburg virus evades interferon responses by a mechanism distinct from Ebola virus. *PLoS Pathog*. 2010;6:e1000721.
8. Reid SP, Leung LW, Hartman AL, et al. Ebola virus VP24 binds karyopherin alpha1 and blocks STAT1 nuclear accumulation. *J Virol*. 2006;80:5156-5167.
9. Volchkov VE, Becker S, Volchkova VA, et al. GP mRNA of Ebola virus is edited by the Ebola virus polymerase and by T7 and vaccinia virus polymerases. *Virology*. 1995;214:421-430.
10. Sanchez A, Trappier SG, Mahy BW, et al. The virion glycoproteins of Ebola viruses are encoded in two reading frames and are expressed through transcriptional editing. *Proc Natl Acad Sci U S A*. 1996;93:3602-3607.
11. Ito H, Watanabe S, Takada A, Kawaoka Y. Ebola virus glycoprotein: proteolytic processing, acylation, cell tropism, and detection of neutralizing antibodies. *J Virol*. 2001;75:1576-1580.
12. Volchkov VE, Volchkova VA, Dolnik O, et al. Polymorphism of filovirus glycoproteins. *Adv Virus Res*. 2005;64:359-381.
13. Mohan GS, Li W, Ye L, et al. Antigenic subversion: a novel mechanism of host immune evasion by Ebola virus. *PLoS Pathog*. 2012;8:e1003065.
14. Martini GA. Marburg virus disease. Clinical syndrome. In: Martini GA, Siegert R, eds. *Marburg Virus Disease*. New York: Springer-Verlag; 1971:1-9.
15. Bausch DG, Nichol ST, Muyembe-Tamfum JJ, et al. Marburg hemorrhagic fever associated with multiple genetic lineages of virus. *N Engl J Med*. 2006;355:909-919.
16. Towner JS, Khristova ML, Sealy TK, et al. Marburgvirus genomics and association with a large hemorrhagic fever outbreak in Angola. *J Virol*. 2006;80:6497-6516.
20. World Health Organization. Ebola haemorrhagic fever in Sudan, 1976. Report of a WHO/International Study Team. *Bull World Health Organ*. 1978;56:247-270.
21. World Health Organization. Ebola haemorrhagic fever in Zaire, 1976. *Bull World Health Organ*. 1978;56:271-293.
22. Khan AS, Tshioko FK, Heymann DL, et al. The reemergence of Ebola hemorrhagic fever, Democratic Republic of the Congo, 1995. Commission de Lutte contre les Epidémies à Kikwit. *J Infect Dis*. 1999;179(suppl 1):S76-S86.
25. Towner JS, Rollin PE, Bausch DG, et al. 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*. 2004;78:4330-4341.
29. Towner JS, Sealy TK, Khristova ML, et al. Newly discovered Ebola virus associated with hemorrhagic fever outbreak in Uganda. *PLoS Pathog*. 2008;4:e1000212.
31. Leroy EM, Kumulungui B, Pourrut X, et al. Fruit bats as reservoirs of Ebola virus. *Nature*. 2005;438:575-576.
32. Towner JS, Pourrut X, Albarino CG, et al. Marburg virus infection detected in a common African bat. *PLoS One*. 2007;2:e764.
34. Kortepeter MG, Bausch DG, Bray M. Basic clinical and laboratory features of filoviral hemorrhagic fever. *J Infect Dis*. 2011;204(suppl 3):S810-S816.
35. Geisbert TW, Young HA, Jahrling PB, et al. Mechanisms underlying coagulation abnormalities in Ebola hemorrhagic fever: overexpression of tissue factor in primate monocytes/macrophages is a key event. *J Infect Dis*. 2003;188:1618-1629.
36. Rollin PE, Bausch DG, Sanchez A. Blood chemistry measurements and D-dimer levels associated with fatal and nonfatal outcomes in humans infected with Sudan Ebola virus. *J Infect Dis*. 2007;196(suppl 2):S364-S371.
37. Ksiazek TG, Rollin PE, Williams AJ, et al. Clinical virology of Ebola hemorrhagic fever (EHF): virus, virus antigen, and IgG and IgM antibody findings among EHF patients in Kikwit, Democratic Republic of the Congo, 1995. *J Infect Dis*. 1999;179(suppl 1):S177-S187.
38. Ksiazek TG, West CP, Rollin PE, et al. ELISA for the detection of antibodies to Ebola viruses. *J Infect Dis*. 1999;179(suppl 1):S192-S198.
39. Towner JS, Sealy TK, Ksiazek TG, Nichol ST. High-throughput molecular detection of hemorrhagic fever virus threats with applications for outbreak settings. *J Infect Dis*. 2007;196(suppl 2):S205-S212.
40. Grolla A, Lucht A, Dick D, et al. Laboratory diagnosis of Ebola and Marburg hemorrhagic fever. *Bull Soc Pathol Exot*. 2005;98:205-209.
41. Zaki SR, Shieh WJ, Greer PW, et al. A novel immunohistochemical assay for the detection of Ebola virus in skin: implications for diagnosis, spread, and surveillance of Ebola hemorrhagic fever. Commission de Lutte contre les Epidémies à Kikwit. *J Infect Dis*. 1999;179(suppl 1):S36-S47.
43. Murphy FA. Pathology of Ebola virus infection. In: Pattyn SR, ed. *Ebola Virus Haemorrhagic Fever*. New York/Amsterdam: Elsevier/North-Holland Biomedical Press; 1978:43-60.
45. Geisbert TW, Jaax NK. Marburg hemorrhagic fever: report of a case studied by immunohistochemistry and electron microscopy. *Ultrastruct Pathol*. 1998;22:3-17.
46. Zaki SR, Goldsmith CS. Pathologic features of filovirus infections in humans. *Curr Top Microbiol Immunol*. 1999;235:97-116.
47. Geisbert TW, Hensley LE, Larsen T, et al. Pathogenesis of Ebola hemorrhagic fever in cynomolgus macaques: evidence that dendritic cells are early and sustained targets of infection. *Am J Pathol*. 2003;163:2347-2370.
48. Hensley LE, Alves DA, Geisbert JB, et al. Pathogenesis of Marburg hemorrhagic fever in cynomolgus macaques. *J Infect Dis*. 2011;204(suppl 3):S1021-S1031.
54. Gear JS, Cassel GA, Gear AJ, et al. Outbreak of Marburg virus disease in Johannesburg. *Br Med J*. 1975;4:489-493.
55. Isaacson M, Sureau P, Courteille G, Pattyn SR. Clinical aspects of Ebola virus disease at the Ngaliema hospital, Kinshasa, Zaire, 1976. In: Pattyn SR, ed. *Ebola Virus Haemorrhagic Fever*. New York/Amsterdam: Elsevier/North-Holland Biomedical Press; 1978:15-20.
56. Geisbert TW, Bausch DG, Feldmann H. Prospects for immunisation against Marburg and Ebola viruses. *Rev Med Virol*. 2010;20:344-357.
57. Falzarano D, Geisbert TW, Feldmann H. Progress in filovirus vaccine development: evaluating the potential for clinical use. *Expert Rev Vaccines*. 2011;10:63-77.
64. Mupapa K, Massamba M, Kibadi K, et al. Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. International Scientific and Technical Committee. *J Infect Dis*. 1999;179(suppl 1):S18-S23.
67. Gunther S, Feldmann H, Geisbert TW, et al. Management of accidental exposure to Ebola virus in the biosafety level 4 laboratory, Hamburg, Germany. *J Infect Dis*. 2011;204(suppl 3):S785-S790.
69. Geisbert TW, Hensley LE, Jahrling PB, et al. Treatment of Ebola virus infection with a recombinant inhibitor of factor VIIa/tissue factor: a study in rhesus monkeys. *Lancet*. 2003;362:1953-1958.
71. Feldmann H, Jones SM, Daddario-DiCaprio KM, et al. Effective post-exposure treatment of Ebola infection. *PLoS Pathog*. 2007;3:e2.
73. Daddario-DiCaprio KM, Geisbert TW, Stroher U, et al. Postexposure protection against Marburg haemorrhagic fever with recombinant vesicular stomatitis virus vectors in non-human primates: an efficacy assessment. *Lancet*. 2006;367:1399-1404.
75. Geisbert TW, Lee AC, Robbins M, et al. Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof-of-concept study. *Lancet*. 2010;375:1896-1905.
76. Warren TK, Warfield KL, Wells J, et al. Advanced antisense therapies for postexposure protection against lethal filovirus infections. *Nat Med*. 2010;16:991-994.
77. Jahrling PB, Geisbert JB, Swearengen JR, et al. Ebola hemorrhagic fever: evaluation of passive immunotherapy in nonhuman primates. *J Infect Dis*. 2007;196(suppl 2):S400-S403.
78. Jahrling PB, Geisbert J, Swearengen JR, et al. Passive immunization of Ebola virus-infected cynomolgus monkeys with immunoglobulin from hyperimmune horses. *Arch Virol Suppl*. 1996;11:135-140.
79. Oswald WB, Geisbert TW, Davis KJ, et al. Neutralizing antibody fails to impact the course of Ebola virus infection in monkeys. *PLoS Pathog*. 2007;3:e9.
80. Dye JM, Herbert AS, Kuehne AI, et al. Postexposure antibody prophylaxis protects nonhuman primates from filovirus disease. *Proc Natl Acad Sci U S A*. 2012;109:5034-5039.
81. Qiu X, Audet J, Wong G, et al. Successful treatment of Ebola virus-infected cynomolgus macaques with monoclonal antibodies. *Sci Transl Med*. 2012;4:138ra81.
82. Olinger GG Jr, Pettitt J, Kim D, et al. Delayed treatment of Ebola virus infection with plant-derived monoclonal antibodies provides protection in rhesus macaques. *Proc Natl Acad Sci U S A*. 2012;109:18030-18035.

References

1. Alibek K, Handelman S. *Biohazard: The Chilling True Story of the Largest Covert Biological Weapons Program in the World—Told from Inside by the Man Who Ran It*. New York: Random House; 1999.
2. Borio L, Inglesby T, Peters CJ, et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA*. 2002;287:2391-2405.
3. United States Government. Possession, Use, and Transfer of Select Agents and Toxins; Biennial Review, Final Rule. In: *Federal Register (77 FR 61084)*. 2012:61083-610115.
4. Feldmann H, Sanchez A, Geisbert TW. Filoviridae: Marburg and Ebola viruses. In: Knipe DM, Howley PM, eds. *Fields Virology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:923-956.
5. Geisbert TW, Jahrling PB. Differentiation of filoviruses by electron microscopy. *Virus Res*. 1995;39:129-150.
6. Basler CF, Wang X, Muhlberger E, et al. The Ebola virus VP35 protein functions as a type I IFN antagonist. *Proc Natl Acad Sci U S A*. 2000;97:12289-12294.
7. Valmas C, Grosch MN, Schumann M, et al. Marburg virus evades interferon responses by a mechanism distinct from Ebola virus. *PLoS Pathog*. 2010;6:e1000721.
8. Reid SP, Leung LW, Hartman AL, et al. Ebola virus VP24 binds karyopherin alpha1 and blocks STAT1 nuclear accumulation. *J Virol*. 2006;80:5156-5167.
9. Volchkov VE, Becker S, Volchkova VA, et al. GP mRNA of Ebola virus is edited by the Ebola virus polymerase and by T7 and vaccinia virus polymerases. *Virology*. 1995;214:421-430.
10. Sanchez A, Trappier SG, Mahy BW, et al. The virion glycoproteins of Ebola viruses are encoded in two reading frames and are expressed through transcriptional editing. *Proc Natl Acad Sci U S A*. 1996;93:3602-3607.
11. Ito H, Watanabe S, Takada A, Kawaoka Y. Ebola virus glycoprotein: proteolytic processing, acylation, cell tropism, and detection of neutralizing antibodies. *J Virol*. 2001;75:1576-1580.
12. Volchkov VE, Volchkova VA, Dolnik O, et al. Polymorphism of filovirus glycoproteins. *Adv Virus Res*. 2005;64:359-381.
13. Mohan GS, Li W, Ye L, et al. Antigenic subversion: a novel mechanism of host immune evasion by Ebola virus. *PLoS Pathog*. 2012;8:e1003065.
14. Martini GA. Marburg virus disease. Clinical syndrome. In: Martini GA, Siegert R, eds. *Marburg Virus Disease*. New York: Springer-Verlag; 1971:1-9.
15. Bausch DG, Nichol ST, Muyembe-Tamfum JJ, et al. Marburg hemorrhagic fever associated with multiple genetic lineages of virus. *N Engl J Med*. 2006;355:909-919.
16. Towner JS, Khristova ML, Sealy TK, et al. Marburgvirus genomics and association with a large hemorrhagic fever outbreak in Angola. *J Virol*. 2006;80:6497-6516.
17. Geisbert TW, Daddario-DiCaprio KM, Geisbert JB, et al. Marburg virus Angola infection of rhesus macaques: pathogenesis and treatment with recombinant nematode anticoagulant protein c2. *J Infect Dis*. 2007;196(suppl 2):S372-S381.
18. Centers for Disease Control and Prevention. Imported case of Marburg hemorrhagic fever—Colorado, 2008. *MMWR Morb Mortal Wkly Rep*. 2009;58:1377-1381.
19. Timen A, Koopmans MP, Vossen AC, et al. Response to imported case of Marburg hemorrhagic fever, the Netherlands. *Emerg Infect Dis*. 2009;15:1171-1175.
20. World Health Organization. Ebola haemorrhagic fever in Sudan, 1976. Report of a WHO/International Study Team. *Bull World Health Organ*. 1978;56:247-270.
21. World Health Organization. Ebola haemorrhagic fever in Zaire, 1976. *Bull World Health Organ*. 1978;56:271-293.
22. Khan AS, Tshioko FK, Heymann DL, et al. The reemergence of Ebola hemorrhagic fever, Democratic Republic of the Congo, 1995. Commission de Lutte contre les Epidémies à Kikwit. *J Infect Dis*. 1999;179(suppl 1):S76-S86.
23. Walsh PD, Abernethy KA, Bermejo M, et al. Catastrophic ape decline in western equatorial Africa. *Nature*. 2003;422:611-614.
24. Leroy EM, Rouquet P, Formenty P, et al. Multiple Ebola virus transmission events and rapid decline of central African wildlife. *Science*. 2004;303:387-390.
25. Towner JS, Rollin PE, Bausch DG, et al. 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*. 2004;78:4330-4341.
26. Jahrling PB, Geisbert TW, Dalgard DW, et al. Preliminary report: isolation of Ebola virus from monkeys imported to USA. *Lancet*. 1990;335:502-505.
27. Barrette RW, Metwally SA, Rowland JM, et al. Discovery of swine as a host for the Reston ebolavirus. *Science*. 2009;325:204-206.
28. Le Guenno B, Formenty P, Wyers M, et al. Isolation and partial characterisation of a new strain of Ebola virus. *Lancet*. 1995;345:1271-1274.
29. Towner JS, Sealy TK, Khristova ML, et al. Newly discovered Ebola virus associated with hemorrhagic fever outbreak in Uganda. *PLoS Pathog*. 2008;4:e1000212.
30. World Health Organization. Ebola, Democratic Republic of the Congo—update. *Wkly Epidemiol Rec*. 2012;87:421.
31. Leroy EM, Kumulungui B, Pourrut X, et al. Fruit bats as reservoirs of Ebola virus. *Nature*. 2005;438:575-576.
32. Towner JS, Pourrut X, Albarino CG, et al. Marburg virus infection detected in a common African bat. *PLoS One*. 2007;2:e764.
33. Taniguchi S, Watanabe S, Masangkay JS, et al. Reston Ebolavirus antibodies in bats, the Philippines. *Emerg Infect Dis*. 2011;17:1559-1560.
34. Kortepeter MG, Bausch DG, Bray M. Basic clinical and laboratory features of filoviral hemorrhagic fever. *J Infect Dis*. 2011;204(suppl 3):S810-S816.
35. Geisbert TW, Young HA, Jahrling PB, et al. Mechanisms underlying coagulation abnormalities in Ebola hemorrhagic fever: overexpression of tissue factor in primate monocytes/macrophages is a key event. *J Infect Dis*. 2003;188:1618-1629.
36. Rollin PE, Bausch DG, Sanchez A. Blood chemistry measurements and D-dimer levels associated with fatal and nonfatal outcomes in humans infected with Sudan Ebola virus. *J Infect Dis*. 2007;196(suppl 2):S364-S371.
37. Ksiazek TG, Rollin PE, Williams AJ, et al. Clinical virology of Ebola hemorrhagic fever (EHF): virus, virus antigen, and IgG and IgM antibody findings among EHF patients in Kikwit, Democratic Republic of the Congo, 1995. *J Infect Dis*. 1999;179(suppl 1):S177-S187.
38. Ksiazek TG, West CP, Rollin PE, et al. ELISA for the detection of antibodies to Ebola viruses. *J Infect Dis*. 1999;179(suppl 1):S192-S198.
39. Towner JS, Sealy TK, Ksiazek TG, Nichol ST. High-throughput molecular detection of hemorrhagic fever virus threats with applications for outbreak settings. *J Infect Dis*. 2007;196(suppl 2):S205-S212.
40. Grolla A, Lucht A, Dick D, et al. Laboratory diagnosis of Ebola and Marburg hemorrhagic fever. *Bull Soc Pathol Exot*. 2005;98:205-209.
41. Zaki SR, Shieh WJ, Greer PW, et al. A novel immunohistochemical assay for the detection of Ebola virus in skin: implications for diagnosis, spread, and surveillance of Ebola hemorrhagic fever. Commission de Lutte contre les Epidémies à Kikwit. *J Infect Dis*. 1999;179(suppl 1):S36-S47.
42. Geisbert TW, Jahrling PB. Use of immunoelectron microscopy to show Ebola virus during the 1989 United States epizootic. *J Clin Pathol*. 1990;43:813-816.
43. Murphy FA. Pathology of Ebola virus infection. In: Pattyn SR, ed. *Ebola Virus Haemorrhagic Fever*. New York/Amsterdam: Elsevier/North-Holland Biomedical Press; 1978:43-60.
44. Murphy FA, Simpson DI, Whitfield SG, et al. Marburg virus infection in monkeys. Ultrastructural studies. *Lab Invest*. 1971;24:279-291.
45. Geisbert TW, Jaax NK. Marburg hemorrhagic fever: report of a case studied by immunohistochemistry and electron microscopy. *Ultrastruct Pathol*. 1998;22:3-17.
46. Zaki SR, Goldsmith CS. Pathologic features of filovirus infections in humans. *Curr Top Microbiol Immunol*. 1999;235:97-116.
47. Geisbert TW, Hensley LE, Larsen T, et al. Pathogenesis of Ebola hemorrhagic fever in cynomolgus macaques: evidence that dendritic cells are early and sustained targets of infection. *Am J Pathol*. 2003;163:2347-2370.
48. Hensley LE, Alves DA, Geisbert JB, et al. Pathogenesis of Marburg hemorrhagic fever in cynomolgus macaques. *J Infect Dis*. 2011;204(suppl 3):S1021-S1031.
49. Ryabchikova EI, Kolesnikova LV, Luchko SV. An analysis of features of pathogenesis in two animal models of Ebola virus infection. *J Infect Dis*. 1999;179(suppl 1):S199-S202.
50. Stroher U, West E, Bugany H, et al. Infection and activation of monocytes by Marburg and Ebola viruses. *J Virol*. 2001;75:11025-11033.
51. Hensley LE, Young HA, Jahrling PB, Geisbert TW. Proinflammatory response during Ebola virus infection of primate models: possible involvement of the tumor necrosis factor receptor superfamily. *Immunol Lett*. 2002;80:169-179.
52. Baize S, Leroy EM, Georges-Courbot MC, et al. Defective humoral responses and extensive intravascular apoptosis are associated with fatal outcome in Ebola virus-infected patients. *Nat Med*. 1999;5:423-426.
53. Geisbert TW, Hensley LE, Gibb TR, et al. Apoptosis induced in vitro and in vivo during infection by Ebola and Marburg viruses. *Lab Invest*. 2000;80:171-186.
54. Gear JS, Cassel GA, Gear AJ, et al. Outbreak of Marburg virus disease in Johannesburg. *Br Med J*. 1975;4:489-493.
55. Isaacson M, Sureau P, Courteille G, Pattyn SR. Clinical aspects of Ebola virus disease at the Ngaliema hospital, Kinshasa, Zaire, 1976. In: Pattyn SR, ed. *Ebola Virus Haemorrhagic Fever*. New York/Amsterdam: Elsevier/North-Holland Biomedical Press; 1978:15-20.
56. Geisbert TW, Bausch DG, Feldmann H. Prospects for immunisation against Marburg and Ebola viruses. *Rev Med Virol*. 2010;20:344-357.
57. Falzarano D, Geisbert TW, Feldmann H. Progress in filovirus vaccine development: evaluating the potential for clinical use. *Expert Rev Vaccines*. 2011;10:63-77.
58. Geisbert TW, Feldmann H. Recombinant vesicular stomatitis virus-based vaccines against Ebola and Marburg virus infections. *J Infect Dis*. 2011;204(suppl 3):S1075-S1081.
59. Sullivan NJ, Sanchez A, Rollin PE, et al. Development of a preventive vaccine for Ebola virus infection in primates. *Nature*. 2000;408:605-609.
60. Jones SM, Feldmann H, Stroher U, et al. Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses. *Nat Med*. 2005;11:786-790.
61. Geisbert TW, Bailey M, Geisbert JB, et al. Vector choice determines immunogenicity and potency of genetic vaccines against Angola Marburg virus in nonhuman primates. *J Virol*. 2010;84:10386-10394.
62. Hensley LE, Mulangu S, Asiedu C, et al. Demonstration of cross-protective vaccine immunity against an emerging pathogenic Ebola virus species. *PLoS Pathog*. 2010;6:e1000904.
63. Falzarano D, Feldmann F, Grolla A, et al. Single immunization with a monovalent vesicular stomatitis virus-based vaccine protects nonhuman primates against heterologous challenge with Bundibugyo ebolavirus. *J Infect Dis*. 2011;204(suppl 3):S1082-S1089.
64. Mupapa K, Massamba M, Kibadi K, et al. Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. International Scientific and Technical Committee. *J Infect Dis*. 1999;179(suppl 1):S18-S23.
65. Akinfeeva LA, Akisonova OI, Vasilevich IV, et al. [A case of Ebola hemorrhagic fever]. *Infektsionnie Bolezni*. 2005;3:85-88 [in Russian].
66. Emond RT, Evans B, Bowen ET, Lloyd G. A case of Ebola virus infection. *Br Med J*. 1977;2:541-544.
67. Gunther S, Feldmann H, Geisbert TW, et al. Management of accidental exposure to Ebola virus in the biosafety level 4 laboratory, Hamburg, Germany. *J Infect Dis*. 2011;204(suppl 3):S785-S790.
68. Huggins J, Zhang ZX, Bray M. Antiviral drug therapy of filovirus infections: S-adenosylhomocysteine hydrolase inhibitors inhibit Ebola virus in vitro and in a lethal mouse model. *J Infect Dis*. 1999;179(suppl 1):S240-S247.
69. Geisbert TW, Hensley LE, Jahrling PB, et al. Treatment of Ebola virus infection with a recombinant inhibitor of factor VIIa/tissue factor: a study in rhesus monkeys. *Lancet*. 2003;362:1953-1958.
70. Hensley LE, Stevens EL, Yan SB, et al. Recombinant human activated protein C for the postexposure treatment of Ebola hemorrhagic fever. *J Infect Dis*. 2007;196(suppl 2):S390-S399.
71. Feldmann H, Jones SM, Daddario-DiCaprio KM, et al. Effective post-exposure treatment of Ebola infection. *PLoS Pathog*. 2007;3:e2.
72. Geisbert TW, Daddario-DiCaprio KM, Williams KJ, et al. Recombinant vesicular stomatitis virus vector mediates postexposure protection against Sudan Ebola hemorrhagic fever in nonhuman primates. *J Virol*. 2008;82:5664-5668.
73. Daddario-DiCaprio KM, Geisbert TW, Stroher U, et al. Postexposure protection against Marburg haemorrhagic fever with recombinant vesicular stomatitis virus vectors in non-human primates: an efficacy assessment. *Lancet*. 2006;367:1399-1404.
74. Geisbert TW, Hensley LE, Geisbert JB, et al. Postexposure treatment of Marburg virus infection. *Emerg Infect Dis*. 2010;16:1119-1122.
75. Geisbert TW, Lee AC, Robbins M, et al. Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof-of-concept study. *Lancet*. 2010;375:1896-1905.
76. Warren TK, Warfield KL, Wells J, et al. Advanced antisense therapies for postexposure protection against lethal filovirus infections. *Nat Med*. 2010;16:991-994.
77. Jahrling PB, Geisbert JB, Swearengen JR, et al. Ebola hemorrhagic fever: evaluation of passive immunotherapy in nonhuman primates. *J Infect Dis*. 2007;196(suppl 2):S400-S403.
78. Jahrling PB, Geisbert J, Swearengen JR, et al. Passive immunization of Ebola virus-infected cynomolgus monkeys with immunoglobulin from hyperimmune horses. *Arch Virol Suppl*. 1996;11:135-140.
79. Oswald WB, Geisbert TW, Davis KJ, et al. Neutralizing antibody fails to impact the course of Ebola virus infection in monkeys. *PLoS Pathog*. 2007;3:e9.
80. Dye JM, Herbert AS, Kuehne AI, et al. Postexposure antibody prophylaxis protects nonhuman primates from filovirus disease. *Proc Natl Acad Sci U S A*. 2012;109:5034-5039.
81. Qiu X, Audet J, Wong G, et al. Successful treatment of Ebola virus-infected cynomolgus macaques with monoclonal antibodies. *Sci Transl Med*. 2012;4:138ra81.
82. Olinger GG Jr, Pettitt J, Kim D, et al. Delayed treatment of Ebola virus infection with plant-derived monoclonal antibodies provides protection in rhesus macaques. *Proc Natl Acad Sci U S A*. 2012;109:18030-18035.
83. Kugelman JR, Lee MS, Rossi CA, et al. Ebola virus genome plasticity as a marker of its passaging history: a comparison of in vitro passaging to non-human primate infection. *PLoS One*. 2012;7:e50316.