Introduction

The term “viral hemorrhagic fever” refers to a clinical syndrome caused by four families of single-stranded RNA viruses: filoviruses (Ebola and Marburg), arenaviruses (with “Old World” Lassa as the main concern, as well as the “New World” South American viruses, Machupo, Junin, and others), bunyaviruses (hantaviruses, Crimean Congo hemorrhagic fever [CCHF] virus, and Rift Valley fever virus), and flaviviruses (yellow fever, dengue, and others). Although the diseases caused by these viruses are frequently considered as a group based on their ability to cause a severe and deadly syndrome, many aspects of the diseases differ, including their natural hosts, geographic locations, annual incidence, prominent clinical features, and case fatality rates. The most important aspect considered in this chapter is the risk of spread in the nosocomial environment, which is primarily a concern for the filoviruses, arenaviruses, and CCHF. Filoviruses and arenaviruses are also considered potential agents of bioterrorism, because they can replicate well in cell culture and are infectious by the aerosol route, as demonstrated in animal studies—properties that are considered necessary for large-scale production and deployment. The large outbreak of Ebola virus disease in West Africa from 2014 to 2016 provides an example of the potential of these diseases to devastate a population, whether or not due to intentional spread,
especially for the diseases that are communicable person to person where medical infrastructure is suboptimal.

**Background**

Hemorrhagic fever viruses are zoonotic pathogens that occur in their geographic settings based on the presence of a host, usually a small rodent or bat. Human cases result from direct or indirect contact with the animal’s excretions, secretions, or blood. For example, African fruit bats are the presumed hosts of Ebola and Marburg viruses, and each of the arenaviruses has a specific rodent (mouse or rat) reservoir. Human infection by hemorrhagic fever viruses occurs by one of four general mechanisms, although the specific risk factors leading to infection may differ, depending on the virus:

1. Inhaling or ingesting excretions or secretions from rodent hosts (urine, feces). This applies to the arenaviruses (Lassa, South American VHF) and bunyaviruses (hantaviruses), predominantly.

2. The bite of an infected mosquito (flaviviruses [yellow fever virus, dengue virus] and bunyaviruses [Rift Valley fever virus]) or tick (flaviviruses [Kyasanur forest disease, Omsk hemorrhagic fever virus] and bunyaviruses [CCHF]).

3. Contact with human or animal blood, body fluids, or tissues. This can occur in the occupational (animal slaughter, laboratory), hospital (filoviruses, arenaviruses, CCHF), or household setting.

4. Exposure to artificially generated aerosols in the context of a bioweapon attack or in the research laboratory setting (most VHFs, except dengue, which is not spread by aerosol, and CCHF viruses, which are difficult to grow in large quantities).

Contact with the virus usually occurs through a break in the skin, contact with mucous membranes, the respiratory tract, or occasionally through ingestion (e.g., consumption of bush meat for Ebola, or multi-
mammate rats for Lassa). The primary means of infection during outbreaks has been through direct person-to-person contact, either in the health care or home environment. Significant spread has also occurred during burial rites where mourners have direct contact with the deceased and has also occurred from reuse of needles/syringes in locations with limited medical resources.

The incubation period for VHFs is generally 1–2 weeks following exposure. For the filoviruses, it is usually considered to be between 2 and 21 days, although most will become ill between the end of the first week and the middle of the second week. Individuals are generally not considered contagious until after the onset of symptoms and become more contagious as signs and symptoms worsen, and viral shedding in body fluids increases. Once ill, an individual should be considered contagious until full recovery and demonstration of an inability to detect virus by PCR. Individuals with filovirus infection may have prolonged shedding (for as long as 2 years) of virus in semen. Viral shedding in other VHF infections is less well characterized, and new information for Ebola is currently being developed through studies of Ebola survivors. The corpses of infected individuals should also be considered hazardous and buried in a manner that minimizes direct contact with the dead body.

Initial replication of Ebola virus occurs in monocytes and macrophages, followed by transport through the blood and lymphatics to target organs. These include the liver and spleen, although high concentrations of virus can be found in all major organs, including the heart and brain. The virus leads to necrosis and lymphocyte depletion as well as impairment of the endothelium and breakdown in the gastrointestinal mucosa.

Clinical illness generally begins with the acute onset of fever, malaise, prostration, skin flushing, conjunctival injection, myalgias, and occasionally sore throat (especially for Marburg and Lassa viruses). The viruses vary significantly in the prominence of other clinical features and severity of illness progression that they cause, but severe illness with any of them can be fatal. After the initial few days, patients infected with the filoviruses may develop significant loss of fluids from vomiting and diarrhea. Dengue fever, the filovirus infections, and Lassa fever frequently present with a maculopapular rash in the first week. Obtundation and encephalopathy occur with the filoviruses and New World arenaviruses.
All of the VHF produce elevations in transaminases, but jaundice and icterus tend to occur more frequently with yellow fever and Rift Valley fever. Third-spacing of fluids leading to significant edema is most prominent with severe Lassa, but can occur with the filoviruses and hantaviruses, especially with the New World hantaviruses, where pulmonary edema is a prominent feature.

During the second week of illness, depending on several factors (viral virulence, route of exposure, inoculum, viremia level, host factors such as age), patients can progress to develop clotting abnormalities and thrombocytopenia that may manifest as oozing from venipuncture sites, petechiae, purpura, and ecchymoses. The viruses that typically lead to bleeding as a more prominent feature (Ebola, Marburg, CCHF, Lassa) are also the ones more frequently associated with nosocomial spread. Patients with severe disease may demonstrate a combination of neurologic and hematologic abnormalities. In rare cases, massive bleeding may occur, usually from the gastrointestinal tract.

Mortality rates for individual VHFs vary considerably. They can range from as high as 80–90% with the Ebola virus (historically referred to as the Zaire species of Ebola virus) or Marburg virus to less than 1% with Rift Valley fever. Among the five species of Ebola virus, the case fatality rates (CFRs) also vary widely, with the CFR for Ebola virus ranging between ~39 and 89%, Sudan virus averaging 53%, Bundibugyo virus 32%, Cote d’Ivoire virus 0% (only a single case), and Reston virus 0%. Reston virus has thus far failed to demonstrated human pathogenicity, despite individual animal handlers having seroconverted.

Despite the syndrome name of viral hemorrhagic fever, a minority of infected individuals will develop frank hemorrhage, and the majority who die do not succumb to blood loss alone. Instead, a sepsis-like clinical syndrome ensues in the more severe cases, with features including loss of vascular hemostasis and increased vascular permeability, decline in mean arterial pressure, lactic acidosis, shock, end organ failure, and death.

**Diagnosis**

The diagnosis of VHF should be considered in patients with an appropriate exposure history and a clinically compatible illness, such as fever
with rash, transaminase elevation, and thrombocytopenia. Some cases, including those due to Lassa and the hantaviruses, as well as those with dengue hemorrhagic shock syndrome, may experience significant vascular leakage, causing hemoconcentration rather than anemia. VHFs, in their early stages, may mimic common diseases, which should be considered in the differential diagnosis in patients who have appropriate travel or other exposure histories. These common diseases include meningococcemia, other causes of bacterial sepsis, rickettsial infections, typhoid, and falciparum malaria. Usually a screening test for VHFs is done with RT-PCR, obtainable through the local or state health department laboratory, with confirmation done by the CDC. Other options for diagnosis, usually only available through containment laboratories, include viral culture, acute and convalescent serology, or immunohistochemistry on autopsy or other tissue specimens, which may need to be done in the absence of licensed tests for many of the pathogens. Patient specimens should be considered extremely hazardous and are best handled in BSL-3 or BSL-4 laboratories, when feasible, depending on the specific pathogen.

**Treatment**

There are no licensed therapies for any VHF; therefore, the primary aspect of care has been supportive: monitoring fluid status closely, monitoring and repleting electrolytes and glucose, minimizing procedures that may cause bleeding, and avoiding medications (such as NSAIDs) that may impair platelet function, use of blood products to correct deficits in hematocrit or other hematologic factors, vasopressors for hypotension, dialysis for renal failure, and ventilators for respiratory failure. The original Marburg outbreaks (in Marburg and Frankfurt, Germany, as well as the former Yugoslavia) in 1967 had a case fatality rate of 23%, which provided an early indicator that care in a developed setting might improve the case fatality rate when subsequent large outbreaks in Angola and the Democratic Republic of the Congo (DRC) led to mortality rates upwards of 80%. Close monitoring and judicious repletion of fluids has led to a significant decline in mortality from dengue hemorrhagic fever/shock syndrome. Using aggressive supportive care measures in
developed-setting intensive care units in the United States and Europe led to lower case fatality rates (18.5%) than those that occurred in African Ebola treatment units, although the individuals cared for in the United States and Europe also received multiple investigational treatments, which may or may not have made a difference. In less developed settings, without ventilator support and renal dialysis, care must be taken to avoid overhydration and the risk of pulmonary edema. Significant strides have been made to bring the standard of care for VHF patients in field environments closer to that provided in developed settings, but there remain challenges in doing so.

Intravenous ribavirin has been used as an experimental treatment for several VHFs, including Lassa hemorrhagic fever, Argentine hemorrhagic fever, CCHF infection, and hemorrhagic fever renal syndrome (caused by Old World hantaviruses). Convalescent antibodies have also been used therapeutically against the arenaviruses, Lassa, and filoviruses, with varying effects.

Several different types of countermeasures are being assessed for use against the filoviruses, including immunotherapeutics (monoclonal and polyclonal antibody preparations), phosphorodiamidate morpholino oligomers (PMOs), lipid-encapsulated small interfering RNAs, small molecule inhibitors, and antiviral nucleoside analogs. Although some appear promising, few have been tested in robust clinical trials. Multiple products were tested, usually against historical controls in the large 2014–16 West Africa Ebola outbreak or given as emergency use investigational new drugs (INDs) in the United States and Europe. No conclusion can be made regarding safety or efficacy with those measures. Use of a cocktail of three monoclonal antibodies, ZMapp™, directed against the glycoprotein on the surface of Ebola Zaire appeared to reduce the case fatality rate in a randomized controlled trial, but the trial did not have adequate numbers to demonstrate statistical significance. In two 2018 outbreaks in the Democratic Republic of the Congo (DRC), several investigational products were approved for compassionate use: ZMapp™, two other monoclonal antibodies (single monoclonal Mab114 and triple monoclonal REGN3470-3471-3479), and the antiviral, remdesivir. As of this writing, a four-arm randomized controlled trial utilizing these prod-
ucts, with ZMapp™ serving as the control arm, is under way at certain Ebola treatment units in the DRC.

**Prevention**

The only VHF with a vaccine licensed in the United States is yellow fever. Investigational vaccines for many of the other VHFs are at varying stages of development, several of which have been tested in humans. For example, there are investigational vaccines for Junin virus (the vaccine is licensed in Argentina) and Rift Valley fever virus that have been used routinely for laboratory workers and have demonstrated protection in animals. Several vaccines have been tested against Ebola virus, and subsequently in humans, including DNA vaccines and adenovirus platforms. One that uses the vesiculostomatitis virus as a vector platform for the Ebola glycoprotein appeared to demonstrate protection against infection when it was used in a ring fashion in exposed household members during the 2014–16 Ebola outbreak in West Africa. It has been offered to health care workers and potentially exposed individuals in two subsequent outbreaks in the DRC in 2018, with more than 133,000 recipients as of this writing in the North Kivu outbreak. It has also been used for postexposure prophylaxis for a laboratory exposure as well as health care exposures in the field, based on the ability to protect nonhuman primates as postexposure prophylaxis.

Several vaccines against Marburg virus are also in development that have demonstrated the ability to protect in a nonhuman primate model, including recombinant VSV-vectored vaccines, adenovirus, and chimpanzee adenovirus-vectored vaccines. Some of these are undergoing early human testing. Some other vaccine platforms, such as DNA vaccines and viruslike particles, are being assessed in both animals and humans.

Outbreaks of VHFs that spread in the nosocomial environment have occurred most commonly in less developed settings, such as Africa or Asia, where health care and public health systems may be less robust. CCHF is an exception, given its wide distribution in developed and underdeveloped settings, and its occasional spread prior to recognition.

In general, in underdeveloped settings, basic hospital infection control modalities may be lacking due to limited resources and a consequent
inability to purchase gloves, gowns, and eye protection, in addition to lack of robust laboratory infrastructure to allow early diagnosis before significant risk of spread occurs. Reuse of unsterilized needles has also led to explosive outbreaks. Significant reductions of spread to health care providers and family members in these environments can be accomplished using basic measures, such as triage, barrier methods to reduce caregiver contact with infectious body fluids, and staff education. Ensuring that caregivers understand the mechanisms of spread and demonstrate proficiency in proper donning and doffing of PPE can significantly reduce risk of spread.

Quarantine

Among the VHF’s, only yellow fever is on the list of internationally quarantinable diseases. Quarantine is usually enforced in countries that have a recent risk of yellow fever outbreaks. Individuals are frequently required to provide documentation showing prior yellow fever vaccination, especially when entering the country from another yellow fever endemic country. Individuals with a syndrome clinically compatible with yellow fever could be quarantined until yellow fever was ruled out, not because of concern over person-to-person spread of the disease but rather due to the possibility of starting an outbreak through mosquito spread from a patient with active viremia.

By presidential executive order in the United States, yellow fever and other viral hemorrhagic fevers, specifically Marburg, Ebola, and CCHF, are quarantinable. Because of concerns of importation of Ebola virus into nonendemic countries during the West Africa outbreaks, the CDC conducted airport screening at those airports that were known hubs for flights returning from West Africa. Individuals with potential exposures were monitored by health departments for a period of 21 days for clinical illness. In some cases, health care providers who had cared for patients in West Africa were quarantined on return to the United States. The US military made the administrative decision to quarantine military personnel for 21 days on return from work in West Africa, even though they did not interact with patients. This was done for administrative purposes and for monitoring for potential other infections (Lassa, malaria).
high-risk laboratory exposures, laboratory workers have also been quar-
antined or actively monitored for 21 days.

In situations involving high-risk exposures, in the household, health care or laboratory setting, it is reasonable to monitor individuals for 21 days. Generally, quarantine is not necessary, because potential spread of the infection does not occur until after the onset of clinical illness, as long as the potentially exposed individuals can be relied on to follow up. They can be educated on recognizing early signs and symptoms, checking their temperature regularly, and maintaining regular contact with public health authorities. Whether or not a health care provider or labora-
orian who has sustained a potential exposure is allowed to continue working during this period of time is a local institutional decision and would depend, in part, on the presumed risk of the exposure. Currently, there is no laboratory test that would identify reliably whether some-
one has been infected prior to the onset of illness. In fact, even after illness onset, current RT-PCR diagnostics may not become positive for 48–72 hours; therefore, repeating an initially negative test is reasonable 72 hours later, depending on the pretest probability that someone has been infected.

Individuals can be risk-stratified according to any potential exposure based on the following table:

**High Risk—exposure to a patient with symptoms:**

- Percutaneous or mucus membrane exposure to blood/body fluids
- Direct contact with a patient without PPE
- Processing lab specimens without PPE
- Direct contact with an infected dead body without PPE

**Some Risk:**

- Close contact with an infected individual in the household or health care/community setting without PPE
- Direct contact while wearing PPE
- Providing any direct patient care (not specifically for patients with a VHF) in a region of country with an active outbreak
Low Risk:

- Brief contact (shaking hands) with a patient in early stages without PPE
- In brief proximity with a patient in early stages (e.g., in the same room)
- Lab processing while wearing appropriate PPE
- Traveling on a plane with an infected patient without any identified high- or moderate- (“some”) risk exposures

The utmost caution must be taken when caring for individuals infected with VHF s that have demonstrated risk of infecting laboratory workers or health care providers (filoviruses, Lassa, South American arenaviruses, CCHF) due to the potential for spread in the nosocomial environment. Individuals with signs or symptoms consistent with a VHF, and a consistent travel/exposure history should be isolated immediately away from other patients and staff and managed as persons under investigation (PU Is). The management of the PUI is addressed in chapter 6 of this manual.

In summary, health care facilities should have practiced procedures for the triage and identification of potentially exposed or ill patients with VHF s. Moreover, they must become familiar with those VHF s requiring quarantine and isolation and develop procedures for the expeditious diagnosis and appropriate disposition of potential VHF patients.