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Abstract
Ebola virus disease (EVD) has existed as a major health concern with devastating and, many times, fatal symptoms. The recent outbreaks of EVD in West Africa and the Democratic Republic of the Congo (DRC) have incited international concern. In this article, the implications of EVD will be discussed including the etiology, transmission, signs and symptoms, diagnosis and treatment of the disease. In addition to this discussion, the manner in which major health care organizations, including the World Health Organization (WHO), are dealing with treating infected patients and containing spread of the disease will be covered.

Key Terms
Africa, West; Congo; Disease Outbreaks; Hemorrhagic Fever, Ebola; Humans; Review Literature; World Health Organization

Introduction

International attention has recently focused on the fatalities caused by the Ebola virus disease (EVD). Previously known as Ebola hemorrhagic fever when first discovered in 1976, EVD has become an epidemic. Two cases occurred simultaneously in Sudan and DRC. The current outbreak has spread outside of Africa and 13,675 laboratory-confirmed cases were reported to WHO and the Centers for Disease Control and Prevention (CDC) between December 2013 and January 2015.[1-6] On Oct. 4, 2014, a case of Ebola virus disease was confirmed in the United States by the CDC and there have, in total, been four cases of EVD treated in the United States to date.[2] With the recent outbreak, fear and questions surrounding EVD have risen; health care professionals have a duty to respond to patient concerns about EVD. This article will discuss the etiology, transmission, symptoms and treatment of EVD.

Disease Etiology

Ebola virus disease is native to regions of Africa. Its natural reservoir is unknown but is believed to be fruit bats.[3,4] There are five species of viruses of the ebolavirus genus, four of which are known to cause disease in humans. Each is named for the geographical location from which it originated. Ebola virus, or Zaire ebolavirus, first identified in DRC, is the species associated with the highest mortality rate, and the species of the current 2014 outbreak.[3,5]

The current outbreak has spread over West Africa in the countries of Guinea, Liberia and Sierra Leone with a total of 22,057 cases reported, and 13,675 of those cases being laboratory confirmed Ebola virus.[6] Because this outbreak has affected areas of large population, the increased rate of transmission makes this the largest outbreak to date. There are four reported cases confirmed in the United States (two travel-associated and two locally acquired) and one travel-associated case in Spain. There were also 66 documented cases of Ebola virus in DRC, but they are not associated with the current outbreak in West Africa. However, with the outbreak in DRC having no new cases since November, the outbreak was declared over on Nov. 21, 2014.[7] Patient zero of the West Africa outbreak was a pregnant woman from Ikanamongo Village who handled bush meat and became ill with symptoms consistent with Ebola virus. She died on Aug. 11, 2014, and several health care workers were exposed to the virus. No one associated with this outbreak reported traveling to the areas of West Africa where the largest outbreak originated.[7] Those who have come in contact with wildlife infected with Ebola virus are at high risk for infection, as the virus can be transmitted through improperly cooked meat or contact with the animal's bodily fluid. Health care workers taking care of infected individuals and people who have had close contact with the patients' bodily fluids are at greatest risk for contracting the infection.

The ebolaviruses are negative-sense ribonucleic acid (RNA) viruses.[5] The exact mechanism for how the virus damages host cells and causes infection has not been clearly studied due to limited research resources in the areas of Africa where the virus is found. However, certain evidence has suggested that the specific glycoproteins on the viral surface envelope attribute to certain progressive properties of the disease. One glycoprotein (GP) contributes to the hemorrhagic symptoms by allowing the virus to insert its contents into monocytes and endothelial cells, causing a release of cytokines leading to inflammation and damage to host blood vessels, respectively. Another GP, sGP, binds to and inhibits neutrophils. This suppression of the host's immune response allows the virus to infect the host unopposed. Furthermore, infected neutrophils transport the virus to the lymph nodes, liver and spleen, which increases the perpetuation of the infection.

Transmission

With limited treatment options for EVD, it is important to reduce the spread and transmission of the virus among hosts because the virus is thought to originate in fruit bats. Individuals are not only warned to avoid contact with these animals, but also other wildlife including monkeys, chimpanzees, gorillas, forest antelope and porcupines.[1] In addition to avoiding the blood, organs, secretions or other fluids from these animals, individuals should refrain from consuming raw meat from any potentially infected species.[8] Live-animal market places are often the culprit of animal to human transmission for a multitude of diseases due to the vast exposure and the mixing of different species. This, combined with poor hand hygiene, results in a greater risk of transmission

of Ebola from animals to humans.[9] It is important to practice meticulous hand hygiene to not only prevent the transmission of the virus from wildlife but also from other humans.[8]

Ebola virus is spread from human to human by direct contact. Individuals may acquire the virus by directly touching any body fluids including blood, semen, feces, saliva, urine and vomit of an infected individual, which then enters through broken skin or a mucous membrane. The virus can also be spread indirectly across surfaces or materials that are contaminated with any such infected body fluids.[1] Perhaps the best way to prevent the transmission from person to person is to avoid any and all blood or body fluids as well as careful hand washing with soap and water or an alcohol-based cleanser.[8] Wearing gloves while handling animals or contaminated individuals is also recommended. Communities in affected areas are advised to avoid funeral or burial rituals that include direct contact of those who have died of Ebola.[1,8] As long as the blood and body fluids of the deceased contain the virus, the individual is considered infectious; thus, facilitating a role in the transmission of the virus.[1] In those areas of outbreak, the WHO suggests quarantining the sick individuals from the healthy individuals and closely monitoring one's health for 21 days if possible exposure has occurred. This 21-day quarantine coincides with the incubation period, or the period of time from infection of the virus until symptoms appear. If no symptoms of Ebola occur within the 21 days, the individual may return to a normal lifestyle.

Health care workers are at significant risk for contracting Ebola virus. Their close contact and direct care with patients infected with the virus increases the potential for transmission of the disease. Due to the nonspecific signs and symptoms of the virus in the beginning stages, the importance of using personal protective equipment in all patient cases regardless of diagnosis is stressed to all health care personnel.[10] Protective devices such as two pairs of gloves, a gown, nonpermeable shoes and a face mask should be put on before entering patient areas and worn during direct care to prevent transmission of the virus Health care facilities are encouraged to place an infected patient in isolation and limit access to those directly caring for that patient. Supplies such as medications, syringes, stethoscopes, thermometers and other frequently used equipment should be kept directly in the room to avoid spreading the virus from one area to another. Visitors should be limited or prohibited during the time of treatment for the infected individual and health care workers should keep a distance of at least one meter from the patient if not providing direct care. The disposal and containment of any needles, linens or wastes should be handled separately from other medical discarded products, and containers should be clearly labeled and disinfected before leaving the isolation area. The WHO stresses the importance of engagement and awareness of the transmission of Ebola for not only health care workers but also for the community as a whole.[1] Case management and containment, as well as thorough adherence to personal protection, may help limit the transmission of Ebola virus for all individuals. Risk reduction should be a central focus regarding the transmission of this disease.

Signs and Symptoms

The incubation period for the virus is extended and varied. The time from infection to symptom presentation is two to 21 days, the average being eight to 10 days.[4,9,11] Once onset of symptoms has occurred, the virus is contagious and can be spread to other people in close contact with the patient.[4]

- Early symptoms after the incubation period can include:[4,9,11,12]
  - sudden onset of fever at least 101°F (38.3°C)
  - malaise
  - headache
  - sore throat
  - muscle pain/weakness
  - lower back pain
  - nausea/vomiting/diarrhea
- Late symptoms are far more severe and fatal including:
  - unexplained hemorrhaging from eyes, ears, nose, mouth or rectum
  - impaired kidney and liver function
  - eye swelling
  - genital swelling
  - extensive blood-containing body rash

Diagnosis

Ebola virus disease is diagnosed using a variety of tests, as early symptomatology, alone, does not distinguish it apart from other diseases such as influenza, typhoid fever, meningitis and malaria. For these reasons, early diagnosis can be difficult; if a person is experiencing early symptoms and has been exposed to the fluids of a person or animal infected with Ebola, or has recently traveled to areas that are experiencing an outbreak, that person should seek medical care immediately. Isolation is imperative and samples from the patient should be tested for confirmation of infection.[11] The tests include:[4,9,11]

- Nonspecific:
  - Complete blood count
  - Liver function tests
  - Coagulation studies
- Specific:
  - Antigen-capture enzyme-linked immunosorbent assay (ELISA)
  - Antibody-capture ELISA
  - Reverse transcriptase polymerase chain reaction (RT-PCR) assay
  - Virus isolation by cell culture
  - Serum neutralization test
  - Electron microscopy

Treatment

There are currently no approved treatments or vaccines for EVD in humans.[13] Isolation of EVD-infected individuals is perhaps the most important component of current therapy. With no approved treatments and high death rates of those infected, prevention of the spread of the virus is key. Current therapy consists only of supportive care.[8] The rapid spread of EVD in the body along with its ability to interfere with blood clotting and electrolyte balance commonly leads to dehydration in infected individuals. Utilization of oral or intravenous electrolyte-containing fluids for rehydration is

important in maintaining appropriate intravascular volume and blood pressure. Electrolyte levels, blood pressure, organ function and patient comfort must be monitored closely. Changes in fluid administration should be made accordingly in order to avoid further complications such as multi-organ failure, shock and death. If multi-organ failure occurs, organ transplant will provide the most successful survival rates. Organ support through dialysis and maintaining adequate blood flow is crucial to keep EVD-infected patients alive and strong enough to fight infection. In cases of disseminated intravascular coagulation, heparin and clotting factors should be given if needed for excess clotting or mass bleeding, respectively. Maintaining oxygen status through ventilation as well as preventing further infection through proper isolation and aseptic technique are critical components in the treatment of EVD-infected patients. The specific supportive care varies from patient to patient based on their presenting symptoms and individualized needs. The key is ensuring the patient is comfortable while restoring optimal organ function to adequately prevent mortality.

While there are no treatments or vaccines currently available for clinical use, there are several under investigation. Compassionate use of these investigational options is controversial because the safety and efficacy has not been adequately studied.[14] However, the WHO states that in certain circumstances of the current outbreak and with specified conditions met, it is ethical to use unproven treatment and/or vaccines in order to provide optimal patient care. These specified conditions include patient groups that will likely have greater benefit than risk while using the agents and those who are "most likely to generate scientific insights that will inform its evidence-based use in the next epidemic."[14] In these cases, investigational options are being used under emergency use protocol. It is important that clinicians know there is a moral obligation to collect and share all data associated with these potential treatments.[15] Recently, the need for urgent development of both preventative and post-exposure treatment has risen. There are several mechanistic treatment options being studied to prevent the spread of EVD, further outbreaks and acts of bioterrorism.[13,16] Potential options include recombinant anti-Ebola monoclonal antibody-based therapy, RNA interference therapy, preventative adenovirus-based vaccines and, most recently, an antiviral oral nucleotide.[8,13]

Mapp Biopharmaceutical has developed ZMapp, a combination of three anti-Ebola monoclonal antibodies produced from Nicotinina plants.[14] The antibodies bind to the proteins of Ebola virus and prevent it from spreading in those already infected. The product first came onto the investigational therapy map in January 2014 and quantity is currently very limited due to minimal manufacturing. ZMapp has not been tested for safety or effectiveness in humans and no randomized controlled trials have been conducted at this point. However, it has been tested in animals and used compassionately in the treatment of EVD-infected American health care workers who returned to the United States from West Africa after the recent outbreak. While some individuals given ZMapp have recovered from the virus, it is unclear whether or not ZMapp played a significant role. Because it has not yet been studied for safety in humans, the risks and side effect profile are unknown. A movement for accelerated studying of ZMapp has been put in place by the company and the U.S. government with hopes of approval for humans by 2015.[8,13] The minimal availability of the product may lengthen the time to approval as it may take months to produce sufficient quantity to be used in research.[14]

A small RNA-interfering molecule developed by Tekmira Pharmaceuticals, TKM-Ebola, is being studied as another potential treatment option for those exposed to Ebola virus.[17] TKM-Ebola is formulated as a stable nucleic acid-lipid particle and works as an inhibitor of an enzyme that catalyzes the viral RNA replication of Ebola. It binds specifically to L polymerase, VP24, and VP35 regions within the RNA sequence. The molecule has performed well in animal studies, but has not yet been approved for safety or efficacy in humans. The U.S. Food and Drug Administration (FDA) recently eased safety restrictions and lifted a hold on the experimental molecule giving it opportunity for advancement in its path to approval.[18] However, human studies have raised safety concerns with the incidence of chills, low blood pressure, nausea and shortness of breath in healthy humans taking TKM-Ebola. This could slow the speed of approval of the drug, but studies are ongoing as Tekmira Pharmaceuticals works to resolve these issues. Animal studies have shown that it takes multiple doses of TKM-Ebola to reach efficacy, which is another concern and potential limitation in its use as EVD therapy.

An emergency investigational new drug application (EIND) by Chimerix, Inc. for brincidofovir has recently been authorized by the FDA.[19] Brincidofovir is an oral nucleotide analog lipid-conjugate. Clinical trials of brincidofovir have progressed to phase III for the use in cytomegalovirus and adenovirus over the past several years. These trials provide data on the safety and dosing of brincidofovir that can be translated to a potential use in EVD. To date, no evidence of kidney or bone marrow toxicity has been found in patients treated with this agent. This lack of toxicity has stimulated further studies of brincidofovir as a promising treatment option. Chimerix is working closely with the FDA to progress in the clinical trials of this agent, as no clinical data has been established yet.

Many mechanisms and molecules have been tested for vaccination purposes. Use of a recombinant vesicular stomatitis virus (VSV) in which the VSV glycoprotein is replaced with a glycoprotein of Ebola virus has shown protection in studies of administration in animals.[16] It is known as rVSV-EBOV. Enzyme-linked immunosorbent assays (ELISA) following administration of rVSV-EBOV have displayed IgG and IgM antibodies against Ebola virus.[17] The adenovirus-based vaccine has shown favorable effects when administered in the live-attenuated form, but shows no protection when administered as an inactivated molecule. This suggests the potency of the vaccine is largely based on the replication of the virus.

The U.S. government has planned "fast-track development" for approval of three additional adenovirus vaccine candidates by the National Institutes of Health (NIH) and Thomas

Jefferson University, Crucell and Profectus Biosciences.[13] GlaxoSmithKline has collaborated with the National Institute of Allergy and Infectious Diseases (NIAID) to derive a replication-defective chimpanzee adenovirus type 3-vectored ebolavirus vaccine (cAd2-ZEBOV) that has rapidly advanced into clinical phase I evaluation, known as the VRC 207 study.[20] The adenovirus serves to carry genetic material derived from the Zaire Ebola species and the Sudan Ebola species. The vaccine delivers one part of the Ebola genetic material to human cells, but rather than replicating it allows the cells receiving the vaccine to express a single Ebola protein, which prompts an immune response. In the VRC 207 study, a monovalent vaccine containing genetic material derived from only the Zaire Ebola species, as well as a divalent vaccine containing genetic material derived from both the Zaire Ebola species and the Sudan Ebola species, began to be tested. The study includes 10 healthy adults receiving the monovalent vaccine and 10 healthy adults receiving the divalent vaccine. Preliminary safety and efficacy data will provide information on the potential benefits and use of this vaccination.

Response from World Health Organization

The passing of Thomas Duncan, the first patient to be treated for Ebola in the United States after having been exposed to the general population, has prompted major discussion on how the United States might deal with containing the disease. Popular media extensively covered this particular case, raising public concern for the possibility for an outbreak in America. As of Aug. 28, 2014, the WHO published its three-point plan with the goal of containing and eliminating Ebola within the next six to nine months, beginning with the countries that are most severely affected.[21] First, the WHO plans to fully respond to all areas where "widespread and intense transmission" are present. The second point is the development and application of full response for those countries that may have Ebola exposure via localized transmission. Finally, the WHO hopes to prepare all countries, especially those that border lands with the highest rates of transmission and those that are major travel hubs, to self-sufficiently deal with the possibility of exposure.

The CDC has recently released a number of online resources consistent with the WHO protocols on disease prevention and readiness, including preparedness checklists to ensure that the United States is ready for a potential outbreak.[22] There are checklists created for emergency medical providers, health care facilities, hospitals, health care coalitions and for the general public. A typical checklist is charged with three primary categories, which are "Prepare to Detect," "Prepare to Protect," and "Prepare to Respond." Within these three primary aims are specific metrics to ensure readiness for the disease. Following the checklist are quick resources for the personnel who would likely be reading the particular checklist. In conjunction with these primary readiness materials, the CDC website also currently contains a regularly updated newsfeed of WHO news and information.

Conclusion

The current outbreak of Ebola is a serious, growing epidemic accompanied with a great amount of worldwide fear. It is important for health care professionals to stay informed and updated as the disease and resulting panic spread. Their potential close contact with infected patients further adds to the need to be ready to respond in accordance with WHO protocol. Early symptoms of the virus can be difficult to differentiate from other common diseases, so it is crucial that anyone who has come in contact with an infected individual seeks medical help as soon as possible if experiencing such symptoms.[11] There are currently no approved treatments or vaccines for EVD in humans, but there are prospects currently in drug development trials that may show promise in treating and preventing EVD.[13] Supportive care for those infected is extremely important as it greatly decreases mortality.[8] The WHO currently has a plan in place to contain the current outbreak.[21] Both the WHO and CDC have step-by-step protocols available on their websites with the intention of helping health care facilities prepare and be able to respond in the event an infected individual needs to be treated at their hospital.[21,22]

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