Ebola Hemorrhagic Fever as a Public Health Emergency of International Concern; a Review Article

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Abstract
Ebola hemorrhagic fever (EHF) was first reported in 1976 with two concurrent outbreaks of acute viral hemorrhagic fever centered in Yambuku (near the Ebola River), Democratic Republic of Congo, and also in Nzara, Sudan. The current outbreak of the Ebola Virus was started by reporting the first case in March 2014 in the forest regions of southeastern Guinea. Due to raising infection rates of over 13,000% within a 6-month period, now is considered as a global public health emergency and in August 8, 2014 the World Health Organization (WHO) has declared the epidemic to be a Public Health Emergency of International Concern. With more than 5000 involved cases and nearly 3000 deaths, this event has turned to the largest and most dangerous Ebola virus outbreak in all around the world. Based on above mentioned, the present article aimed to review the virologic characteristics, transmission, clinical manifestation, diagnosis, treatment, and prevention of Ebola virus disease.

Key words: Hemorrhagic fever, Ebola; health; emergency responders; virology; infection control

Introduction:
Ebola hemorrhagic fever (EHF) was first reported in 1976 with two concurrent outbreaks of acute viral hemorrhagic fever centered in Yambuku (near the Ebola River), Democratic Republic of Congo, and also in Nzara, Sudan. There have been almost 20 other outbreaks that involving nearly 2500 cases happened before 2014. With the exception of a single case identified in the Republic of Côte d'Ivoire in the 1990s, all of them were reported in sub-Saharan Africa involving the Sudan, Gabon, Uganda, and Democratic Republic of Congo (1). But the current outbreak (2014), which is the largest one ever documented, is the first recorded outbreak of Ebola in West Africa (2). The previous largest outbreaks of Ebola virus was identified in Uganda in 2000–2001 which caused by Sudan ebolavirus (SUDV) subtype. This outbreak resulted in nearly 400 cases, 216 of which were laboratory confirmed and had 53% overall case-fatality rate (3). The 25th known outbreak of the Ebola Virus was started by reporting the first case in March 2014 in the forest regions of southeastern Guinea and due to raising infection rates of over 13,000% within a 6-month period, now is considered as a global public health emergency and in August 8, 2014 the World Health Organization (WHO) has declared the epidemic to be a Public Health Emergency of International Concern (2, 4). Thereafter, Ebola virus has spread through the West Africa and appeared in Senegal, Sierra Leone, Liberia, Nigeria, and now it has been reported in Spain and United State of America, too. With more than 5000 involved cases and nearly 3000 deaths, this event has turned to the largest and most dangerous Ebola virus outbreak in all around the world (5). Based on above mentioned, the present article aimed to review the virologic characteristics, transmission, clinical manifestation, diagnosis, treatment, and prevention of Ebola virus disease.

Virologic characteristics
Ebola virus is a lipid enveloped ribonucleic acid (RNA) virus belongs to the flavivirus family and has been known since 1976. It consists of five different sub-types and Ebola virus Zaire sub-type (ZEBOV) was the first one which was recognized in the Democratic Republic of Congo. The current Ebola virus has 97% homology with ZEBOV (6, 7). Other subtypes include Bundibugyo (BDBV), SUDV, Côte d'Ivoire or Tai Forest (TAFV) and
Reston ebolaviruses (RESTV). Ebola hemorrhagic fever (EHF), caused by ZEBOV, has the highest fatality (57%–90%), followed by SUDV (41%–65%) and BDBV (40%) and these three sub-types are responsible for the large outbreaks occurred recently in Africa. However to date, RESTV infection has been observed in animals in Asia and as asymptomatic in humans, while TAFV has only been identified in 2 human cases, both of them were non-fatal (4, 8, 9).

Transmission
Some authors claimed that a 44-year-old man suffering from malaria was the first identified fatal case of EHF by using a contaminated needle for administration of parenteral chloroquine in the Democratic Republic of Congo (previously named Zaire) in 1976 (1). On the other hand, some researches indicated that the first person become infected through contact with an infected animal (4). Fruit bats that live in Guinea and neighboring countries are considered as the natural hosts of Ebola viruses and other mammals serving as accidental hosts. This virus has been implicated as one of the major causes of decreasing African chimpanzee and gorilla populations in recent decades (1, 10, 11). Ebola is one of the zoonotic viruses that can lead to a high fatal disease in human beings. Humans are also one of the accidental hosts and can be infected through close contact with blood and bodily fluids of another infected case (including humans and animals), either by direct contact or indirectly from a contaminated environment. It seems that mosquitoes and other insects do not play a role in the virus transmission and also it is not spread through the air (1, 4, 10). Ebola virus has high transmissibility and virulence so that less than 10 viral particles are enough for becoming infected. The incubation period range is from 2-21 days (average 5-6). Fortunately the disease is not transmissible until the patient becomes symptomatic, but it continues to be contagious, even postmortem (2, 12). Family and healthcare providers caring the Ebola patients are at the highest risk for becoming infected because of their possible contact with contaminated blood or body fluids. So the virus can easily spread if reasonable preventive precautions are not taken (4).

Clinical Manifestation
The patient should be evaluated for EHF with both suggestive symptoms, including unexplained hemorrhage and risk factors within 3 weeks prior such as contacting with suspected or confirmed EHF cases or travel to an endemic area (2). EHF is a fatal disease (mortality rate 50%-70%) that can be occurred 2-21 days after exposure to the virus. The initial clinical presentation is non-specific. Early clinical symptoms of EHF include abrupt onset of fever, fatigue, myalgia and headache followed by progressive gastrointestinal symptoms such as anorexia, nausea, and abdominal discomfort accompanied with vomiting and diarrhea within 1-2 days. This process can lead to intravascular volume depletion and furthermore profound electrolyte disorders, hypoperfusion, shock, and multi-organ failure (acute respiratory, liver, and renal failure) within a few days. The “hemorrhage” of phrase “Ebola hemorrhagic fever” is a late manifestation, usually occurs as gastrointestinal bleeding, conjunctival hemorrhage, epistaxis, and hemorrhagic rash. Some others believe that these symptoms occur only in a minority of patients, that is why they use “Ebola Virus Disease” instead (1, 2, 5, 9, 10, 12-16). Complete blood count usually shows leucopenia and thrombocytopenia but hemoglobin levels almost never decrease significantly. Intravascular volume depletion and hypoperfusion are manifested by metabolic lactic acidosis and renal insufficiency. Massive diarrhea associates with profound hypokalemia and hemagglutopenia spread of virus to the liver and spleen leads to hepatocellular injury marked by elevated liver enzymes (2, 5, 12-14). Analysis of coagulation profile shows increased prothrombin and partial thromboplastin times (PT and PTT) accompanied by detection of fibrin degradation products in the occurrence of disseminated intravascular coagulation (DIC) (6).

Diagnosis
Except Ebola virus, there are other types of viruses that can cause hemorrhagic fever, including Crimean-Congo hemorrhagic fever virus, Marburg virus, Lassa virus, and emerging ones such as Lujo virus. These viruses have particular public health importance because of their spread ability to careers and healthcare workers, difficulties in their rapid recognition, the lack of effective specific therapeutics, and high fatality rate, (10). Definitive diagnosis of a clinically suspected case of Ebola virus infection requires laboratory confirmation. In EHF, viremia develops after the fever and takes up to 3 days to confirm the diagnosis by proper laboratory evaluation. It’s necessary to collect serum, plasma, or whole blood samples of at least 4 milliliters, refrigerated or on ice, to the appropriate health department for further testing. Early diagnosis is confirmed via detecting viral antigens by using polymerase chain reaction (PCR) or enzyme-linked immunosorbent assay (ELISA) on the blood sample. Later during the disease course, antibodies against the virus such as Immunoglobulin M (IgM) and Immunoglobulin G (IgG), can also be detected. If the test results be positive, local and state health departments should be notified immediately. However, because of the extreme biohazard risk, using antigen- or antibody-based assays or PCR testing should be performed in a biosafety level 4 laboratories. It is clearly more possible in developed countries where such laboratories are provided (1, 2, 17). Centers of Disease Control and Prevention (CDC) has performed standardized enzyme-linked immunosorbent assay (ELISA) for detection of Ebola virus specific antibodies. This test has high sensitivity and can be used for detecting antibodies in human beings even after
10 years exposing to the virus (6).

**Treatment**

There is no specific antiviral agent or vaccine against Ebola viruses. Therefore supportive care is the most important aspect of its management. Aggressive prevention of intravascular volume depletion is critical to avoid life-threatening complications by using proper fluid therapy, oxygen therapy, correcting profound electrolyte abnormalities, and preventing the complications of shock such as acid–base derangements. Treatment of other infections, if they occur, and close monitoring of vital signs and regular biochemical and blood gas check should also be done. These proceedings are considered as the foundation of critical care medicine and should be applied in both resource-rich and resource-constrained settings. With improving supportive cares, EHF outcomes may also improve. Symptom control with taking narcotics and benzodiazepines were often reported as the end-of-life therapy in some patients (2, 5, 14). Variety of chemotherapeutic agents have been tested for different stages of development which the recombinant human activated protein C and recombinant nematode anticoagulant protein c2 are also among them. One drug identified as ZMAPP, has been taken to several patients, however it still remains unclear if it is really effective or not. Therefore, there is no Food and Drug Administration (FDA) approved agent exist against Ebola (4, 6, 18-23). Figure 1 shows the latest CDC algorithm regarding emergency department evaluation and management for possible Ebola infected patients.

**Prevention**

The current outbreak of EHF demonstrated more on the importance of prevention strategies. Health care workers have represented a considerable proportion of all infected cases. So educating and training of universal precautions, risk assessment, and use of personal protective equipment for all medical staff is crucial. Patients initially identified as having a possible viral hemorrhagic fever should be isolated until the results of their specific diagnosis are obtained from reference laboratories. It is important to not delay in diagnosis and treatment of more common diseases, such as malaria or typhoid, during this period. Follow-up of contact cases is essential for infection containment in the event which the patient tests are positive. Special equipped ambulances and trained staff should be prepared to do transferring when they are needed (1, 10, 24). Early diagnosis and rapid laboratory confirmation with isolation of patients and following their contacts, as well as accessing to protective equipment and environmental decontamination are the mainstay of prevention.

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**References:**

Figure 1: Shows the latest CDC algorithm regarding emergency department evaluation and management for possible Ebola infected patients.