

Ebola viral disease: What should be done to combat the epidemic in 2014?

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Abstract: Ebola virus disease (EVD) was defined first in 1976. Since then, more than 24 epidemics have been reported from Africa, predominantly with the Zaire species. On 21 March 2014, the current West Africa outbreak was reported by the World Health Organization, the largest one ever recorded. The Congo epidemic was reported in July 2014. It was considered that the two epidemics had unrelated origins with 96.8% identical genomic sequence of the virus. EVD outbreaks occurred in areas with limited resources but it has a potentially global effect due to the possibility of imported infection and the potential misuse of the virus as a bioweapon agent. Although EVD is a zoonotic disease with the reservoir of fruit bats, human-to-human transmission is essential in the spread of the infection. The case-fatality rate of EVD was reported as 70.8%. There is no approved prophylaxis, effective treatment, or licensed vaccine. Early diagnosis and isolation of the patients, contact tracing, appropriate use of personal protective equipment, and adherence to the guidance for safe funeral practices constitute the essential requirements to control the epidemics. This article provides a review of the literature regarding the characteristics and management of EVD outbreak.

Key words: Viral disease, Ebola viral disease, outbreak, control of epidemic

1. Introduction

The Ebola virus, which belongs to the viral family *Filoviridae*, causes Ebola virus disease (EVD) and is endemic to Central Africa. Fruit bats of the family Pteropodidae are the recognized reservoir of the virus (1,2). Five distinct species of the virus are the Zaire, Sudan, Ivory Coast, Bundibugyo, and Reston agents, which are all limited to Sub-Saharan Africa (except the Reston virus, which was defined in the Philippines and has not caused any symptomatic disease in humans) (3,4). The Ebola virus is an important threat to the world due to the possibility of misuse as a biological weapon and imported infections as a result of increased international travelers (5). There have been 25 outbreaks reported to date including the current outbreak: four in 1976–1979, six in 1994–1996, nine in 2000–2008, and six after 2011 (6,7). The current outbreak involves the Zaire species of the virus and is occurring in West Africa (Guinea, Liberia, Sierra Leone, Senegal, and Nigeria); it started in Guinea in late 2013 and was confirmed by the World Health Organization (WHO) in March 2014. It is the largest outbreak to date with a total of 10,141 cases (5692 of which were confirmed) and 4922 deaths by 25 October 2014 (4,8). Twenty-seven of them were reported as travel-associated cases and localized transmissions: 20 cases from Nigeria, 4 from the United

States, and one each from Senegal, Mali, and Spain. The outbreaks of EVD in Senegal and Nigeria were announced on 17 and 19 October 2014, respectively. A national EVD outbreak is considered to be over when double the maximum incubation period (42 days) has passed after the last patient became laboratory-negative for EVD (8). On 26 July 2014, another EVD epidemic was reported from the Congo in Equatorial Africa, which had a zoonotic origin different from the current epidemic in West Africa. By 21 October 2014, there had been 67 cases of EVD (38 laboratory-confirmed cases and 49 deaths) reported in the Democratic Republic of the Congo. When the genome sequence of the virus was analyzed, it was observed that it shared 96.8% identity with the current West Africa Ebola virus variant and 99.2% identity with the variants of the 1995 outbreak in the Congo (7,9). The case-fatality rate of EVD is very high, ranging between 20% and 90% depending on the virus species (1,2). The highest mortality rate (60%–90%) is seen with the Zaire Ebola virus species, followed by the Sudan Ebola virus species (40%–60%). The Bundibugyo virus species has caused only one outbreak to date, with a 25% mortality rate. Case-fatality rate was reported as 70.8% in the current outbreak when the first 9 months of data were evaluated (10). Systemic inflammatory response syndrome is a characteristic of

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EVD, which causes vascular impairment, disseminated intravascular coagulopathy, and immune deficiency and results in multiorgan failure, shock, and death in severe cases (5). Awareness of the disease's symptoms and transmission routes, use of active surveillance systems, rapid identification of cases, contact tracing, isolation of patients, and appropriate use of personal protective equipment (PPE) are the main factors to prevent outbreaks. Community education is also critical (6). In this review, we aimed to identify the clinical characteristics and patient management of EVD in light of the literature.

2. Clinical findings

The Ebola virus causes severe hemorrhagic fever with acute onset of nonspecific flu-like symptoms after the incubation period (range: 2–21 days; approximately 6 days for percutaneous transmission and 10 days for contact exposure). Fever, weakness, malaise, headache, diarrhea, and vomiting are nonspecific symptoms that cause misdiagnosis of the patients, such as diagnoses of typhoid fever or malaria in the early period of the outbreak (4,). Fever (39–40 °C) and relative bradycardia are frequent findings seen in the early phase of the disease. Nonpruritic maculopapular rash is usually seen between 5 and 7 days on the trunk and upper arms, ending with desquamation in the convalescence period. Mucosal hemorrhage (especially in the conjunctiva), petechiae, ecchymosis, and oozing from venipuncture sites can be observed in patients. Massive hemorrhage, typically in the gastrointestinal system, is usually observed only in fatal cases (11,12). Anorexia, vomiting, diarrhea, and abdominal pain constitute the gastrointestinal system findings (5). Scleral icterus is a rare manifestation that was reported in the literature (11,12). According to the reported data of the first 9 months of the current outbreak, fever (87.1%), fatigue (76.4%), vomiting (67.6%), diarrhea (65.6%), loss of appetite (64.5%), headache (53.4%), and abdominal pain (44.3%) were the common symptoms in the early phase of EVD. Unexplained bleeding was reported in only 18.0% of cases. Mortality predictors were reported as old age (≥ 45 years, OR: 2.47), hemorrhages (epistaxis, OR: 8.02; bleeding gums, OR: 6.69; bleeding at injection site, OR: 6.51; blood in urine, OR: 5.14), and a number of signs and symptoms such as coma or unconsciousness (OR: 4.59), difficulty swallowing (OR: 2.22), hiccups (OR: 2.15), conjunctivitis (OR: 2.03), and confusion (OR: 2.00) (10). Fatal cases typically have more severe clinical signs in the early phase of infection and death is usually seen between days 6 and 16 due to major hemorrhages, septic shock, and multiorgan failure (4,5). Fatal cases do not produce specific antibodies (immunoglobulin M and G), which can usually be detected in the first week of the disease in survivors. Recovery of the signs and symptoms

of survivors is typically observed around days 6 to 11 due to the effect of humoral antibodies. Survivors have protracted convalescence (weeks to months) with the findings of weakness, fatigue, headache, and loss of weight and hair (5,11).

3. Laboratory findings

Leukopenia (as low as 1000 cells/ μ L) with lymphopenia and granulocytosis is a typical finding of EVD, especially in the early phases. As the illness progresses, leukocytosis can be observed due to the increase in immature granulocytes and atypical lymphocytes. Thrombocytopenia (50,000–100,000 cells/ μ L) is the early finding of the disease. Occurrence of elevated liver function enzymes is one of the common findings of EVD, and the AST value is higher than ALT. The mean level of AST is 7–12 times higher than ALT in fatal cases and 2–4 times higher in survivors (5,11). Renal function test scores may increase after the first week of clinical onset, which is usually normal in the early phase of the disease. Renal impairment is more frequent in fatal cases (11–13). Disseminated intravascular coagulation is usually seen in EVD patients. Increases in partial thromboplastin time, prothrombin time, bleeding time, and plasma D-dimer levels of patients with EVD were reported in literature (5). D-Dimer levels of patients with EVD in the 2000 outbreak of Sudan were reported to be significantly higher in fatal cases (13). Increased risk of miscarriage was reported among infected pregnant women (5).

4. Transmission and prevention of EVD

Recent studies show that fruit bats are the reservoir for Ebola virus species. The initial transmission to humans may be the result of contact with bats' or sick nonhuman primates' excretions in forested areas and/or consumption of infected animals (6). The virus enters the body via inhalation, through abrasions of the skin or mucosal areas, or via the parenteral route. Outbreaks usually occur as a consequence of human-to-human transmission of the virus via contact with body fluids of symptomatic patients and/or infected corpses (3,10,14). The estimated reproduction number (R_0), which shows the average number of secondary cases after exposure to a primary case in an uninfected population, was reported as 1.71 for Guinea, 1.83 for Liberia, and 2.02 for Sierra Leone in the first 9 months of the current epidemic. When the R_0 value of the infection is observed to be higher than 1, it means that the spread rate of the infection will be high, which is directly proportional to the level of R_0 . In addition, the mean length of time between the onset of the symptoms and hospitalization was reported to be 5.0 ± 4.7 days in the current EVD epidemic, which indicates the period of infectiousness in the community. However, since

patients are infectious only after they have symptoms, early diagnosis and isolation of symptomatic patients is essential for limiting transmission in the community. Contact tracing and follow-up surveillance of all contacts are other critical factors to control the further spread of the infection. The suggested time for the follow up of contacts is 21 days, which is the maximum incubation period (10,15). Currently, due to the increasing number of international air travelers, contact tracing involving passengers who traveled with an infected individual is another important issue. Although there is no known transmission case recorded in an aircraft for EVD to date, it is recommended that co-travelers who have had direct contact with the index case and/or sat adjacent to the index case (side by side or in the immediate back/front row) should be traced. Crew members who served the index case and staff who cleaned the relevant section of the plane should also be traced (16). Healthcare workers (HCWs) constitute the other important high-risk group for transmission and should use PPE appropriately (4). A total of 318 EVD cases among HCWs, with 151 deaths, were reported by September 2014 (10). Inadequacies in hospital infrastructure, limited numbers of HCWs per person, and absence of sufficient PPE (gloves, face masks, gowns, etc.) are the main causes of the transmission of EVD to HCWs in the current outbreak. Not only the establishment of isolation units but also the provision of sufficient PPE is necessary to reduce transmission (17). Gloves, impermeable gowns, medical masks, eye protection, and fluid resistant shoes, such as rubber boots, are the suggested PPE. While applying aerosol-generating procedures, the wearing of FFP2 or N95 respirator masks is also suggested. In addition, training of HCWs about the appropriate procedure of putting on and removing PPE and applying hand hygiene is essential, as detailed in the guidelines of the WHO (18). Reusing contaminated medical equipment is another transmission route of infection in healthcare settings, which should be avoided (3). Since dead bodies are infectious, burial practices should include the decontamination of deceased bodies with 1:10 sodium hypochlorite solution and placement in a plastic body bag (19). In addition to all these precautions, education in healthcare settings and in the community (especially how to recognize the suspected/probable cases, symptoms, routes of transmission, and protection) is mandatory to control epidemics (15).

5. WHO/Centers for Disease Control and Prevention (CDC) case definitions for EVD

According to the case definitions for EVD reported by the WHO, a suspected case was defined as follows:

1) Any ill person (alive or dead) who had high fever with abrupt onset and had contact with a suspected/

probable or confirmed patient with EVD or contact with a sick/dead animal.

2) Any person with abrupt onset of high fever and a minimum of three of the following symptoms or findings: headache, loss of appetite, anorexia, vomiting, diarrhea, lethargy, hiccup, stomach pain, aching muscles or joints, swallowing and/or breathing difficulties, unexplained bleeding, or any sudden death due to an unknown cause.

A probable case was defined as any suspected patient who had an epidemiologic link to a confirmed case in the previous 21 days with no laboratory confirmation. A confirmed case was defined as a suspected or probable case with a positive reverse transcription polymerase chain reaction (RT-PCR) test result for Ebola virus at the reference laboratory (10,20). On 27 October 2014, the CDC updated the case definitions to include the category of "Person Under Investigation (PUI)" as a person who has consistent findings or symptoms and risk factors as follows:

1. Increased body temperature or subjective fever or symptoms, involving fatigue, severe headache, myalgia, vomiting, diarrhea, abdominal ache, or unexplained bleeding; and

2. An epidemiologic risk factor within 21 days before the initiation of symptoms.

A "Confirmed Case" is a PUI with a laboratory confirmation of Ebola virus infection (21).

6. Diagnosis

Clinical assessment according to case definitions is necessary for the diagnosis of EVD. Malaria and typhoid fever are the most important infections that should be considered in differential diagnosis, followed by shigellosis, leptospirosis, yellow fever, and Chikungunya fever (22). RT-PCR and antigen detection with ELISA are the basic assays for laboratory diagnosis of acute EVD infection, which can be positive in blood from day 3 of the onset of symptoms until days 7–16. IgM and IgG ELISA tests are the assays that can be used to detect specific antibodies. IgM antibodies can be determined from day 2 after the onset of symptoms and decrease to undetectable levels 30–168 days after infection. Specific IgG antibodies appear after 6–18 days of the onset of the symptoms and can be detectable for years (5,22,23). Laboratory assays can be performed after the inactivation of the virus in the material by different methods (heat inactivation, gamma irradiation, denaturation of the proteins with guanidinium isothiocyanate) (5,24,25).

7. Case management and potential therapies and vaccines

Symptomatic and supportive therapies are the basic procedures for case management in addition to isolation of the patient. Since it is frequently mistaken with malaria and

other endemic infections, empiric treatment of malaria, broad-spectrum antibiotics, analgesics, and antipyretics should be initiated immediately while obtaining the confirmed diagnosis. Intravenous fluid volume and electrolyte balance should be monitored and replaced. Complications of the disease at a later stage, such as bleeding, renal failure, secondary bacterial infections, and shock, are other disorders that should also be managed (5). There are many investigations about potential therapies and vaccines for EVD. It has been suggested that convalescent plasma that includes antibodies of EVD survivors might prevent the disease. However, its effect is controversial and further investigation is necessary. Antibody treatments, such as ZMapp and hyperimmunoglobulin, are offering hope, but their clinical effectiveness is still not known. Favipiravir/T-705 and interferons are other agents that have shown effectiveness in animals but have not been studied

for Ebola in humans yet. The chimpanzee adenovirus serotype 3 vaccine (ChAd3) and recombinant vesicular stomatitis virus vaccine have been studied in animals and have shown effectiveness, but there are no safety studies in humans so far. Fifteen thousand doses of EVD vaccine may be available by the end of 2014 according to the results of the studies (26).

8. Conclusion

As a consequence, the current outbreak in West Africa is not only a problem for that area but is also an important challenge to the whole world. Since there is no available prophylaxis, vaccine, or effective treatment for EVD, it is necessary to break the human-to-human transmission cycle. Education of HCWs and the broader community about infection control precautions is essential to combat outbreaks.

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