Review Article

Overview of Ebola virus disease in 2014

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Abstract

In late December 2013, a deadly infectious epidemic, Ebola virus disease (EVD), emerged from West Africa and resulted in a formidable outbreak in areas including Guinea, Liberia, Sierra Leone and Nigeria. EVD is a zoonotic disease with a high mortality rate. Person-to-person transmission occurs through blood or body fluid exposure, which can jeopardize first-line healthcare workers if there is a lack of stringent infection control or no proper personal protective equipment available. Currently, there is no standard treatment for EVD. To promptly identify patients and prevent further spreading, physicians should be aware of travel or contact history for patients with constitutional symptoms.
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1. Introduction

On December 26, 2013, a 2-year-old child in the remote Guinean village of Meliandou fell ill with a mysterious malady characterized by fever, black stools, and vomiting.[1] The small male child passed away from his illness 2 days thereafter. In the months following that case, thousands of people living in Guinea, Liberia and Sierra Leone also died with similar symptoms.[2] The pathogen of the outbreak was identified, and recalled the tragic circumstances of more than 30 years ago — the onset of the Ebola virus.

In 1976, a new filovirus was identified in Zaire (now the Democratic Republic of Congo [DRC]) and was named Ebola after the River Ebola in the DRC. The mortality rate caused by the virus was around 90%.[3,4] Although medical facilities have improved over the years, the mortality of this outbreak in West Africa was still more than 50% in 2014.[5] The emergence of the outbreak of EVD in West Africa shared common features with the outbreak in 1976. Both were caused by *Zaire ebolavirus* and began in rural forest communities. Critically-ill patients were brought to provincial hospitals with vague systemic presentations, causing hospital staff to be unaware of the risks of being exposed to patient blood and body fluids without proper protection and which inevitably worsened the outbreaks.[1,6] Furthermore, cases associated with locally infected patients who travelled out of the West Africa region had been identified in Senegal, Nigeria, Spain, and even the United States.[7] Due to the pervasive travel and general international contacts implicit in globalization, as well as the popularity of tourism, EVD is most certainly a threat to Taiwan.

2. Virology

Ebola virus is an enveloped, negative single strand RNA virus. It belongs to the virus family *Filoviridae*, also including Cuevavirus and Marburg virus, with the characteristic

filamentous or branching convoluted shape.[8] EVD is classified as a fifth-category notifiable communicable disease in Taiwan, along with such other diseases as the Marburg virus.[9] The genus Ebola viruses are divided into five subtypes: Zaire (EOBV), Sudan (SUDV), Bundibugyo (BDBV), Tai Forest (TAFV) and Reston (RESTV).[10] All but RESTV cause disease in humans and each subtype has different biologic characteristic and virulence.[8,11]

The exact origin, location, and natural reservoir of Ebola virus remain unclear, although it is believed that the virus is zoonotic and fruit bats may be the culprits of dissemination.[8] According to epidemiological investigations, the previous area of EVD outbreak overlapped with fruit bat territory.[12] In Africa, *Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata* are considered the natural hosts of the Ebola virus.[8] In addition, some primates, such as apes or monkeys, can also get infected.[13] In general, if people have contact with, or eat the infected reservoir of an infected animal, they may get infected.[14] However, in order for any larger scale person-to-person transmission to occur (as in the past Ebola outbreak), the virus would have to spread through the blood or body fluids, including but not limited to urine, saliva, sweat, feces, vomitus, breast milk, and semen, as well as via contaminated objects like needles and syringes.[3,14] The Ebola virus is not spread through the air or by water, or by food in general. Currently, there is no evidence that mosquitoes or other insects can transmit Ebola virus.[14] Once a person is infected by the Ebola virus, there is no infectivity until the onset of symptoms.[15] The infectious doses for Ebola virus disease is relatively high, frequently in the range of 10^7 to 10^8 pfu/g.[8] The viral load increases as the disease becomes worse. Therefore, the infectivity of patients with Ebola virus disease is not as high as expected in the early stage. However, the amount of viral particles originating from patients at the later stage of Ebola is extremely high and will easily infect persons without proper protection.

3. Epidemiology

The first case of the Ebola virus disease was recognized in 1976, and caused an outbreak in northern Zaire. The subtype was named Zaire Ebola Virus (EOBV).[3] At the same time, another unrelated virus, which resulted in epidemics in south Sudan, 850 kilometers away from Zaire, was identified as Sudan Ebola Virus (SUDV).[16] SUDV recurred in the same area of Sudan in 1979.[17] After two decades of silence, Ebola hemorrhagic fever re-emerged in 1994−1997 in DRC (formerly Zaire) and Gabon.[18,19] During the early 21st-century, smoldering outbreaks of EOBV and SUDV were reported in Uganda[20] and Congo.[21] The mortality rates for EOBV and SUDV were on average 80−90% and 50%, respectively.[8] In 1994, a new serotype of Ebola virus was identified from a patient and a chimpanzee in Ivory Coast. The serotype, affecting a single non-fatal case, was first named the Côte d'Ivoire ebolavirus and then renamed the Tai Forest Virus (TAFV).[10,22] The fourth Ebola virus subtype, Reston virus (RESTV), which had resulted in nonhuman primate outbreaks, was first identified in the

United States during 1989−1990.[23] In 1992, another outbreak occurred in Italy. Both events were related to the importation of monkeys from the Philippines.[24] In 2008, there was a noticeable increase of cases of porcine reproductive and respiratory syndrome (PRRS) caused by RESTV in the Philippines and China. The disease was characterized by high mortality in sows and piglets. Fortunately, although the animal farmer workers might become seropositive, the infection was asymptomatic and there were no human deaths.[11] In 2007, an outbreak of hemorrhagic fever occurred in Uganda and was caused by the fifth Ebola virus subtype, Bundibugyo virus (BDBV).[20] Another outbreak caused by BDBV occurred in DRC in 2012.[25] The mortality rate was around 40%, lower than the previous two serotypes.[8] It is worth mentioning that in 2014, the outbreak of hemorrhagic fever in West Africa and DRC were caused by EOBV, although the two outbreaks were unrelated.[26] Owing primarily to the mechanisms of travel-related and healthcare transmission, the EVD was also found in United State, Spain, Mali, Senegal and Nigeria (Table 1). Fortunately, with the assistance of sufficient infection control, the EVD outbreaks in Senegal and Nigeria were declared over on October 17 and October 19, 2014, respectively.[7]

Table 1
Chronological list of outbreaks of Ebola virus disease in Africa.

Years	Country	Subtype	Estimated mortality rate
1976	Zaire (Democratic Republic of Congo)[a]	Zaire	88%
	South Sudan	Sudan	53%
1977	Zaire	Zaire	100%[b]
1979	South Sudan	Sudan	65%
1994	Gabon	Zaire	60%
	Côte d'Ivoire (Ivory Coast)	Tai Forest	0%[b]
1995	Democratic Republic of Congo (formerly Zaire)	Zaire	81%
1996	Gabon[c]	Zaire	57%
	Gabon[c]	Zaire	75%
	South Africa	Zaire	50%
2000	Uganda	Sudan	53%
2001	Gabon	Zaire	82%
	Republic of Congo	Zaire	75%
2002	Republic of Congo	Zaire	90%
2003	Republic of Congo	Zaire	83%
2004	South Sudan	Zaire	41%
2007	Democratic Republic of Congo	Zaire	71%
	Uganda	Bundibugyo	25%
2008	Democratic Republic of Congo	Zaire	47%
2011	Uganda	Sudan	100%[b]
2012	Uganda[c]	Sudan	36%[d]
	Democratic Republic of Congo	Bundibugyo	36%[d]
	Uganda[c]	Sudan	50%[d]
2014	West Africa (including Guinea, Liberia, Sierra Leone, and Nigeria)[e]	Zaire	36%
	Democratic Republic of Congo[f]	Zaire	74%

[a] The first episode of Ebola outbreaks.
[b] Only one defined case.
[c] Different time and towns in the same country.
[d] Laboratory confirmed cases only.
[e] Defined cases were also found in United States, Spain, Mali and Senegal.
[f] Unrelated to outbreak in West Africa.

4. Clinical Manifestations

EVD has an incubation period of 2 to 21 days (mean, 4−10 days), and the infection is acute without any carrier status. Symptoms usually begin with a flu-like syndrome, including sudden onset of high fever, chills and myalgia. Multiple systems may be involved, including gastrointestinal (anorexia, nausea, vomiting, abdominal pain, diarrhea), respiratory (chest pain, dyspnea, cough), vascular (conjunctival injection, postural hypotension, edema) and neurologic (headache, confusion and coma) manifestation. A macropapular rash associated with varying severity of erythema and desquamate can often be noted by day 5−7 of the illness. Hemorrhagic manifestations arise during the peak of the illness and include petechiae, ecchymoses, uncontrolled oozing from venepuncture sites, mucosal hemorrhages, and post-mortem evidence of visceral hemorrhagic effusions. Hemorrhages can be severe but are present in less than half of the affected patients. Those patients with fatal disease develop clinical signs early during infection and die typically between day 6 and 16 with hypovolemic shock and multi-organ failure. Among non-fatal cases, patients have fever for several days and improve typically around day 6 to 11.[4,8]

The Ebola virus enters the host through mucosal surfaces, skin defect, or by parenteral introduction.[3,8,16,19] The virus has a broad cell tropism, affecting monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes, adrenal cortical cells, and several types of epithelial cells. Initially, the virus replicates in monocytes, macrophages, and dendritic cells. Due to the subsequent carriage of these cells, the virus disseminates to regional lymph nodes through the lymphatic system and to the liver and spleen through the blood.[8,27−30] Various degrees of hepatocellular necrosis resulted in decreased synthesis of coagulation and other plasma proteins. The phenomenon is consistent with disseminated intravascular coagulation (DIC) and may be related to hemorrhagic tendencies.[4,8,16,28] But, massive blood loss is infrequent and, if present, is mainly limited to the gastrointestinal tract. Even in these cases, the amount of blood loss is not sufficient to cause death.[3,8] Adrenocortical infection and necrosis causes impaired steroid synthesis and may lead to hypotension and hypovolemia, which plays an important role in the late stages of hemorrhagic fever.[4,8,28]

5. Diagnosis

The EVD usually presents as an acute viral prodrome and many differential diagnoses should be considered, such as malaria, typhoid fever, yellow fever and meningococcal meningitis, which are also endemic diseases in Africa.[4,8] Therefore, it is important to trace the travel and exposure history when approaching a suspected patient returning from an endemic area.

Laboratory diagnosis for EVD should be performed in a well-equipped laboratory with up to biosafety level 4 biocontaminant facilities for viral culturing. In Taiwan, EVD is a fifth-category notifiable communicable disease and should be reported to the Taiwan Centers of Disease Control (CDC) within 24 hours. The characteristics that define reported EVD include: 1. Clinical conditions which met any one of the following: (1) acute febrile illness (≥38°C) (2) headache, myalgia, nausea, vomiting, diarrhea and abdominal pain, (3) bleeding with unknown reason, and (4) sudden death with unknown reason; 2. Laboratory conditions, with any of the following: (1) clinical specimen (throat swab or skin biopsy) that were isolated and identified as Ebola virus, (2) clinical specimen that show positive by reverse transcription-polymerase chain reaction (RT-PCR), and (3) serology (enzyme link immunosorbent assays, IgM and IgG) positive; 3. Epidemiologic conditions, with any of the following 21 days before onset of symptoms: (1) history of travel from or living in the endemic area of EVD, (2) exposure of blood, body fluids or discharge pollutants from possible or defined cases, (3) history of contact with bats, rodents, or primates in endemic area of EVD, (4) operate the specimen of EVD in a laboratory. Once the case fulfills clinical and epidemiologic conditions or any laboratory benchmark, the patient should be reported to the Taiwan CDC within 24 hours. If the first report is negative but the patient's symptoms persist, a second examination should be conducted three days later in case of false negative.[31]

Routine laboratory data in the early stage of EVD are similar to that observed in common viral infection: leucopenia (as low as 1000 cells/L), left shift with atypical lymphocytes, thrombocytopenia (50,000−100,000 cells/L), and elevated liver enzymes (aspartate aminotransferase typically exceeding alanine aminotransferase). Prothrombin and partial thromboplastin times are extended and fibrin split products are detectable, indicating DIC. Leukocytosis may occur if complicated with secondary bacterial infection.[4,8] Considering the elevated need for patient and laboratory safety, physicians should carefully evaluate the necessity of frequent blood examination to prevent bleeding from the venipuncture site and the risk of unexpected laboratory exposure.

6. Treatment

Currently there is no standard treatment for EVD. The main strategies presently employed are symptomatic and supportive care, such as preserving fluid and electrolytes balance, maintaining oxygen saturation and blood pressure, and treating complications such as secondary infections.

Because of the high mortality rate of EVD, many investigational treatments are underway (Table 2):

1. Zmapp: This experimental drug, developed by Mapp Biopharmaceutical, Inc., is a combination of three humanized murine antibodies generated by Ebola virus infected mice, and subsequently produced in tobacco plants. In animal studies, forty-three percent of infected mice survived with Zmapp treatment.[32] It has been used experimentally for some patients in the 2014 West Africa Ebola outbreak, and several people survived. However, because no randomized controlled clinical trials have been undertaken, it remains inconclusive whether ZMapp is effective for people suffering from EVD.[33,34]

Table 2
Investigational modalities and vaccines for Ebola virus disease treatment.

Drug	Mechanism	Effect
Zmapp	Combined antibody binds to and inactivates virus	- Protects monkeys infected with Ebola virus - Seven people on "compassionate use", two died
Convalescent therapy	Passive immunization (neutralizing antibodies, serum from recovered Ebola patients)	- Protective effect, *in vitro* - Therapeutic effect, in rodents but fails in non-human primates
Antiviral drug		
Ribavirin	Interferes with capping of viral mRNA	- Not recommended due to severe adverse effects
Lamivudine	A nucleoside analogue that interferes gene replication	- No survival benefit demonstrated in EVD
Favipiravir	Broad effect antiviral compound that inhibits a viral enzyme	- Protects mice with Ebola. -Phase III trials in human with influenza
Vaccine		
cAd3	Segments of genetic material from two Ebola virus species delivered by a chimpanzee virus	- Imminent phase I clinical trials
rVSV	A gene from Ebola loaded in a weakened version of vesicular stomatitis virus	- Prevents lethal infection in non-human primates

2. Convalescent therapies (plasma from recovered Ebola patients): This strategy had been used to support passive immunization. In 1976, the treatment had been used for a woman with EVD in Zaire. Initially, her symptoms improved but she eventually passed.[35,36] Like ZMapp, there have been no randomized controlled clinical trials for this disease management strategy. Nevertheless, as the Ebola epidemic remains largely uncontrolled, the World Health Organization (WHO) was approached by several donors, foundations, public health agencies, and development partners to offer guidance and advice for this and other strategies.

3. Antiviral drugs: Ribavirin and lamivudine had been tried as a means to treat Ebola virus disease. However, ribavirin was not recommended due to severe adverse effects that were observed.[8,37] Furthermore, there was no obvious survival benefit for lamivudine treatment.[33] Another experimental anti-viral drug, favipiravir, was developed by Fujifilm, Japan, initially for treating influenza virus infection. This drug could prevent a lethal outcome in the animal study. Given the ongoing challenges that Ebola virus presents, further human studies are ongoing.[34]

4. Vaccine: There are currently two vaccine candidates, cAd3-EBOV (cAd3) and rVSVΔG-EBOV-GP (rVSV), and both are under investigation. The cAD3 vaccine is in Phase I trial and the rVSV vaccine had been shown to prevent lethal infection in non-human primates. However, their short and long-term effectiveness against the Ebola virus in humans requires further evaluation.[34]

7. Prevention

Since there are no standard treatments for EVD, it is important to avoid infection or further spreading of the virus. For the general population, if travelling to any endemic area of EVD (such as Guinea, Liberia, and Sierra Leone), contact with or consumption of any wild animal is strongly dissuaded. For those with a history of travel from any endemic area in the past three weeks, body temperature should be monitored for up to 21 days.[38] For healthcare workers, personal protective equipment should be properly put on and taken off while caring for possible or defined patients. Safety needles are recommended for venipuncture or blood examination. Once exposed to blood or body fluids of the unprotected patient, healthcare workers should thoroughly flush the exposure site with water or soap. Afterward, body temperature should be monitored for 21 days. The defined case should be isolated in a negative pressure isolation room or, alternatively, a single room with independent sanitary wares. Under the circumstances of two negative results within a single 48 hour period, isolation status could be removed.[39] In the event of death attributed to EVD, corpses should be burned within 24 hours. Men who have recovered from the disease can still transmit the virus through their semen for up to 7 weeks after recovery.[40]

The Ebola virus is moderately thermolabile and susceptible to many chemical agents, such as 3% acetic acid, 1% glutaraldehyde, alcohol-based products, and dilutions (1:10 to 1:100) of 5.25% household bleach (sodium hypochlorite) for more than 10 minutes, and calcium hypochlorite (bleach powder).[41] According to the WHO recommendations, a potentially hazardous blood spill or body fluid environment could be cleaned up with 1:10 dilution of 5.25% household bleach for 10 minutes. For surfaces that may corrode or discolor, the recommendation was careful cleaning to remove visible stains followed by contact with a 1:100 dilution of 5.25% household bleach for more than 10 minutes. Clothing or drape with severe contamination should be burned if safe cleaning is not feasible.[38]

In conclusion, Ebola virus infection is a lethal zoonotic disease with a high mortality rate. Currently, there is no standard treatment for the disease and supportive treatment was the only available strategy. Although many experimental trials are underway, the best we can do to prevent a rampant outbreak in Taiwan is stringent infection control operations. Clinicians should consider the possibility of Ebola virus infection in persons with travel or exposure history with the incubation period presenting constitutional symptoms. First-line healthcare providers should also be acutely aware of appropriate infection prevention measures for patients whose travel, country of origin or other contacts may make them the subject of further inquiry and investigation now or in the future.

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