1. Introduction

Ebola virus (EBOV) belongs to the family Filoviridae, the genus *Ebolavirus*, and frequently causes fatal infection in humans[1]. EBOV disease (EVD) may show multiple, serial, and nonspecific-disease symptoms including high fever, headache, vomiting, anorexia, diarrhea, and aching muscles[1-4]. Unexplained bleeding in the eyes, nose, gums, and gut occurs in the advanced stages[1-4]. The first outbreak of EVD was reported in 1976 in the Democratic Republic of the Congo. Until 2013, most outbreaks occurred in the Central African region, including Zaire, Sudan and Uganda. However, between March and October 2014, over 10,000 cases of EVD have been recorded in West Africa, such as in Guinea, Liberia, Sierra Leone, and Nigeria, and a few hospital or secondary infections of EVD have occurred in Spain and the United States of America. EVD is presently one of the world’s most feared diseases. In this literature review, we describe the epidemiology, clinical features, diagnosis, and treatment of EVD.
Table 1. EVD first emerged in 1976 in the Democratic Republic of Congo (DRC) and at around the same time in Sudan. Among these epidemic areas, 318 cases were recorded in DRC (case fatality rate [CFR]: 88%) and 284 cases in Sudan (CFR: 53%). As the first reports of the epidemic occurred near the Ebola River, DRC, the disease became known as Ebola hemorrhagic fever (EHF)[7,10], and two different species of EBOV were confirmed: EBOV-Zaire (EBOV-Z) and EBOV-Sudan (EBOV-S). In 1977, one fatal case due to EBOV-Z was reported in Zaire, and EBOV-S subsequently reemerged with 34 cases, 22 of which were fatal, in Sudan in 1979.

No further cases were recorded until 1994, when a new species of EBOV was confirmed in a non-fatal case in the Ivory Coast and named EBOV-IC. One case was confirmed who had traveled from Liberia to Sierra Leone and had antibodies to EBOV, suggesting existence of EBOV-IC in Liberia[11]. These episodes suggest that EBOV had spread from areas in Central Africa to West Africa. In 1995, EVD due to EBOV-Z reemerged in the DRC[12]. An estimated 315 cases and 250 deaths (CFR: 81%) occurred during this large epidemic. The EBOV-Z species identified was shown to have a close genetic relationship with the strains isolated in 1976 in Zaire[13]. EBOV-S then emerged in Uganda during 2000-2001, resulting in an estimated 425 cases and 224 deaths (CFR: 53%). The EBOV species identified could be clearly placed among the EBOV-S strains isolated in 1976 in Sudan[14,15]. In 2004, an EBOV-S outbreak of 17 cases and 7 deaths (CFR: 41%) was reported in Yambio County, South Sudan. The index case had butchered a monkey, and human-to-human transmission was mainly through direct contact[16]. Outbreak of EBOV-Z occurred in the Republic of Congo in 2002-2003 with 143 cases (128 deaths, CFR: 89%) and in the DRC in 2007, with 264 suspected cases and 187 deaths (CFR: 71%) recorded[17,18]. In November 2007, a new EBOV species, designated Bundibugyo ebolavirus (EBOV-B), was identified in Western Uganda, and 149 suspected cases and 37 deaths had been reported by January 2008 as the outbreak neared conclusion[19]. In the 2008 Ebola outbreak, there were 32 cases including 15 deaths (CFR: 47%) in Kasaï Occidental Province in the DRC[20,21]. In May 2011, a patient with suspected EHF died after contacting EBOV-S in Luwero District, Uganda[22], and the following year an outbreak among 11 patients resulted in 4 deaths from EHF in Kibaale District[23]. Another EVD outbreak occurred in the DRC

| Year          | Outbreak location            | Species          | Human cases | Report number of human cases | Report number of deaths among cases | CFR (%) |
|---------------|------------------------------|------------------|-------------|------------------------------|------------------------------------|---------|
| 1976          | Democratic Republic of Congo (formerly Zaire) | Zaire            | 318         | 280                          | 88                                 |         |
| 1976          | Sudan (South Sudan)          | Sudan            | 284         | 151                          | 53                                 |         |
| 1976          | England                      | Sudan            | 1           | 0                            | 0                                  |         |
| 1977          | Zaire                        | Zaire            | 1           | 1                            | 100                                |         |
| 1979          | Sudan (South Sudan)          | Sudan            | 34          | 22                           | 65                                 |         |
| 1989          | USA                          | Reston           | 0           | 0                            | 0                                  |         |
| 1990          | USA                          | Reston           | 4 (asymptomatic) | 0                     | 0                                  |         |
| 1989-1990     | Philippines                  | Reston           | 3 (asymptomatic) | 0                     | 0                                  |         |
| 1992          | Italy                        | Reston           | 0           | 0                            | 0                                  |         |
| 1994          | Gabon                        | Zaire            | 52          | 31                           | 60                                 |         |
| 1994          | Côte d'Ivoire (Ivory Coast)  | Tai Forest       | 1           | 0                            | 0                                  |         |
| 1995          | Democratic Republic of the Congo | Zaire         | 315         | 250                          | 81                                 |         |
| 1996 (January - April) | Democratic Republic of the Congo | Zaire        | 37          | 21                           | 57                                 |         |
| 1996-1997 (July - January) | Gabon | Zaire | 60 | 45 | 74 |
| 1996          | South Africa                 | Zaire            | 2           | 1                            | 50                                 |         |
| 1996          | USA                          | Reston           | 0           | 0                            | 0                                  |         |
| 1996          | Philippines                  | Reston           | 0           | 0                            | 0                                  |         |
| 1996          | Russia                       | Russia           | 1           | 1                            | 100                                |         |
| 2000-2001     | Uganda                       | Sudan            | 425         | 224                          | 53                                 |         |
| October 2001-March 2002 | Gabon | Zaire | 65 | 53 | 82 |
| October 2001-March 2002 | Republic of the Congo | Zaire | 57 | 43 | 75 |
| December 2002-April 2003 | Republic of the Congo | Zaire | 143 | 128 | 89 |
| November-December 2003 | Republic of the Congo | Zaire | 35 | 29 | 83 |
| 2004          | Sudan (South Sudan)          | Sudan            | 17          | 7                            | 41                                 |         |
| 2004          | Russia                       | Zaire            | 1           | 1                            | 100                                |         |
| 2007          | Democratic Republic of Congo | Zaire | 264 | 187 | 71 |
| December 2007-January 2008 | Uganda | Bundibugyo | 149 | 37 | 25 |
| November 2008 | Philippines                  | Reston           | 6 (asymptomatic) | 0 | 0 |
| December 2008-February 2009 | Democratic Republic of the Congo | Zaire | 32 | 15 | 47 |
| May 2011      | Uganda                       | Sudan            | 1           | 1                            | 100                                |         |
| June-October 2012 | Uganda | Sudan | 11 |
| June-November 2012 | Democratic Republic of the Congo | Bundibugyo | 36 | 13 | 36 |
| November 2012-January 2013 | Uganda | Sudan | 6 | 3 | 50 |
| March 2014-Present | Various countries | Zaire | 15113 | 5406 | 36 |

* These data are based on earlier reports[1-28]; CFR: Case fatality rate.
in 2012, and 13 of the 36 laboratory-confirmed cases died[24,25]. None of the abovementioned outbreaks had epidemiologic links[1].

3. Initial EVD epidemiology in 2014

An epidemiologic investigation of laboratory-confirmed cases indicated that the first fatality of the current 2014 outbreak occurred in December 2013 in Guinea[4]. The patient was a 2-year-old child, and 8 other deaths were confirmed between December 2013 and February 2014 in the same village (Méliandou village, Guéckédou Prefecture). The disease may have spread from some of these patients to others in neighboring prefectures such as Macenta, Nzérékoré, and Kissidougou[4]. Guéckédou and Macenta prefectures are bordered to the north by Liberia and Sierra Leone. The epidemiologic investigation reported 15 fatal laboratory-confirmed EVD cases[4]. EBOV-Z was identified as the causative agent and phylogenetic analysis suggested that an independent cluster had formed from the previously identified EBOV strains from the DRC and Gabon[4].

4. EVD epidemics in West Africa in 2014

The relatively small EVD outbreaks in Guinea may have spread to neighboring countries such as Liberia and Sierra Leone[26]. As of 16 November 2014, 15,113 EVD cases have been reported (confirmed, probable and suspected cases) in eight countries since the epidemic began. Among them, 5,406 deaths have occurred (CFR: 35.8%)[27]. As of November 2014, EVD cases in Guinea, Liberia, and Sierra Leone amount to 1,971 (CFR: 60.4%), 7,069 (CFR: 41.9%) and 6,073 (CFR: 20.6%), respectively[27], with some cases being reported further afield in Mali, Nigeria, and Senegal[27]. Four EVD patients reported in the United States of America and one in Spain have all involved in medical personnel or those who worked in the epidemic areas[27]. Detailed geometric data are shown in Figure 1.

5. Virology of EBOV

EBOV belongs to the family Filoviridae and the genus Ebolavirus[1,10]. Five EBOV species have been identified: EBOV-Z, EBOV-S, EBOV-IC, EBOV-B, and Reston ebolavirus. The prefix of the family name “filo” originates from the Latin word for thread or string. Virions have multiple morphological forms of very long filamentous rods or compact convoluted shapes (diameter around 80 nm, length 800-14,000 nm)[1]. The EBOV genome is a single negative-sensed RNA (genome size 19 Kb). The virions contain 7 proteins: nucleoprotein, viral proteins 24, 30, 35, and 40, glycoprotein (GP), and L protein. The structure of the genome is similar among the species, but phylogenetic analysis has shown the species have formed independent lineages with wide genetic divergence (Figure 2). Notably, the virulence of each species may differ markedly from the others[1,3]. For example, EVD cases due to EBOV-Z and EBOV-S show high CFRs of over 70% and 50%, respectively, while the CFR for EBOV-B is around 27%[3,28]. Reston ebolavirus may have low or no virulence in humans, but it is thought that the virus is highly virulent in simians[1].

Phylogenetic analysis based on the GP gene sequences of EBOV detected in patients from the current epidemic areas have been confirmed as EBOV-Z strains and they have close genetic relationships.
However, the genetic properties of these strains may be different from typical EBOV-Z\cite{29}. In addition, the CFR for the present EBOV-Z epidemics is relatively low (around 40%-50%) compared with typical EBOV-Z\cite{30}, while in a recent report with laboratory confirmed cases, the CFR is 74% in Sierra Leone\cite{31}. The reason for the difference in virulence among the strains is not known.

6. Transmission routes

Although the life cycles of EBOV species are not precisely known, the natural hosts (reservoirs) of EBOV are thought to be a species of fruit bat\cite{32,33}. It is known that EBOV can transmit from bats to some species of simians\cite{9}, so EBOV-infected bats and simians may be an infectious source of EBOV when handled or consumed by humans\cite{9}. It is thought that almost all human-to-human EBOV infections are due to direct contact with blood and/or body fluids (e.g., saliva, mucus, vomit, feces, sweat, tears, breast milk, urine, and semen) from symptomatic/dead patients\cite{7}. Thus, extreme care must be taken when handling the body fluids of patients with EVD to avoid infection\cite{7}. Indeed, two thirds of the EVD cases in the Guinea epidemic during 2014 may have contacted the virus via unprotected (or unsuitably protected) contact with infected corpses during Guinean burial rituals.

7. Clinical features of EVD

EVD tends to cause the severest form of viral hemorrhagic fever in humans. Most EVD cases manifest as a sudden onset of influenza-like symptoms, such as high fever, chills, malaise, and myalgia\cite{1,3,6,34}, which may develop to systemic gastrointestinal symptoms (vomiting and diarrhea) and respiratory (chest pain and cough), vascular (conjunctival injection and edema), and neurological (headache, confusion, and coma) symptoms\cite{1,3,6}. Hemorrhagic symptoms may follow, including petechiae, ecchymosis, and uncontrolled mucosal hemorrhage\cite{1,3,6}. These symptoms can resemble other diseases however, such as malaria, cholera, typhoid fever, meningitis, and other viral hemorrhagic fevers. Cause of death is usually from multiple organ failure due to these complications\cite{1,3,6}.

General laboratory data are nonspecific to EVD\cite{1,3,35}. In the early phase of the disease, leukocytopenia and lymphocytopenia may be evident in peripheral blood, and subsequent neutrophilia and thrombocytopenia are often seen\cite{1,3}. In addition, elevation of ectopic enzymes such as aspartate transaminase and alanine aminotransferase is common\cite{1,3}. Abnormalities may occur in the blood coagulation system, such as prolonged prothrombin and partial thrombin time. At the end stage, secondary bacterial infections such as pneumonia may develop\cite{1,3}. In nonfatal cases, a high fever may continue for about 5 to 9 d, but symptoms improve around 7 to 10 days after onset\cite{1,3,36}. At that time, a humoral antibody response may be noted. There are no specific symptoms in the early stage of EVD; thus, laboratory confirmation is essential\cite{1}. RT-PCR and/or immunological methods (ELISA) are generally used for detection, as with other viral infections\cite{1}.

8. Present status of therapeutic drug developments for EVD

At present, there is no approved definitive treatment, such as vaccines or anti-viral drugs, for EVD\cite{1,3,34}. Therefore, symptomatic treatment methods including infusion of electrolyte and/or antibiotics are mainly used\cite{1,3}.
Two promising candidate vaccines against EVD have been reported to date. The US National Institute of Allergy and Infectious Diseases and GlaxoSmithKline line have developed one candidate EVD vaccine, cAd3-ZEBOV[37]. The vaccine is a chimpanzee-derived adenovirus vector with an Ebola virus gene inserted. The second candidate, rVSV-ZEBOV, has been developed by the Public Health Agency of Canada in Winnipeg[38]. The availability of these drugs for clinical use is eagerly awaited.

The experimental drug ZMapp has been administered in 3 cases so far. It contains three monoclonal antibodies (mAbs) that are designed to neutralize EBOV[39]. The mAb cocktail binds to and neutralizes the GP protein of EBOV and has been shown to prevent infection in monkeys[39]. ZMapp was administered to 2 American EVD patients who were infected while treating EVD patients in Liberia during the recent epidemic[40], and both completely recovered from serious EVD; however, another Spanish patient treated with the same drug has died[40]. It is too early to tell how effective this experimental treatment will be.

Among the anti-viral drugs under development, a nucleic acid analog known as “favipiravir” may be applicable to the treatment of EVD[41]. It is a prodrug of a purine nucleoside analog, ribavirin, that inhibits the synthesis of viral RNA through the action of RNA-dependent RNA polymerase (RdRp) of influenza virus[42]. Some mechanisms of viral RNA synthesis are similar between EBOV and influenza viruses[43], so it is expected that the drug will have similar effects on the RNA synthesis of EBOV. Indeed, significant effects against EVD have been reported in mice[43]. We may therefore see favipiravir being tried clinically in the present EVD epidemic.

9. Conclusion

We have described current knowledge of EVD based on a review of the literature. With the knowledge we have thus far, it appears that it will be difficult to predict the extent and outcomes of EVD epidemics in the future. However, about 30 years ago, human immunodeficiency virus (HIV) infection suddenly emerged and spread throughout the world, and now, thanks to continuous efforts by the medical community, effective treatment methods against HIV infection are available, although the disease cannot yet be eradicated. EBOV and EVD are poorly understood at present, but there is hope that effective treatment methods to combat EVD will soon be developed.

Conflict of interest statement

We declare that we have no conflict of interest.

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