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A Detail Review: Ebola Virus

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Abstract:

Ebola virus disease (EVD) is a highly lethal viral illness, with a mortality rate that varies between approximately 30% and 90%. The initial Ebola Virus Disease (EVD) outbreak was documented during the 1970s in Zaire, which is presently known as the Democratic Republic of the Congo. Prior to 2013, the majority of epidemics were concentrated in the Central Africa region, specifically in Zaire, Sudan, and Uganda. During the period from March to October 2014, more than 10,000 cases of Ebola Virus Disease (EVD) were documented in West Africa, specifically in Guinea, Liberia, Sierra Leone, and Nigeria. Additionally, a small number of hospital or secondary infections of EVD were reported in Spain and the United States of America. Currently, EVD is regarded as one of the most dreaded diseases worldwide. This literature review provides a comprehensive overview of the epidemiology, clinical aspects, diagnosis, and therapy of Ebola Virus Disease (EVD).

1. Introduction

The Ebola virus (EBOV) is a member of the Filoviridae family and the Ebolavirus genus. It often leads to lethal infections in humans[1]. Ebola virus disease (EVD) can present with a range of symptoms that occur in succession and are not specific to the disease. These symptoms may include elevated body temperature, severe headache, vomiting, loss of appetite, diarrhoea, and muscle pain[1-4]. Haemorrhaging in the eyes, nose, gums, and gastrointestinal tract is observed in the latter stages[1-4]. The initial occurrence of Ebola Virus Disease (EVD) was documented in 1976 in the Democratic Republic of the Congo[5]. Subsequent to then, there have been documented instances of minor outbreaks of Ebola Virus Disease (EVD) in several nations in Central Africa, such as Sudan and Uganda[1,6]. It is believed that there have been approximately 2350 cases of EVD between the 1970s and 2013. Consequently, the disease might be considered as prevalent in certain regions of Central Africa.

In March 2014, a widespread occurrence of Ebola Virus Disease (EVD) was documented for the first time in West Africa, namely in Guinea. The disease quickly extended to nearby countries such as Liberia and Sierra Leone, resulting in a severe epidemic. This

has resulted in significant health issues, both locally and globally, prompting the World Health Organisation (WHO) and some governments to implement health surveillance and containment strategies[8,9]. In this article, we provide a comprehensive overview of the past and present outbreaks of Ebola Virus Disease (EVD), including its epidemiology, clinical manifestations, diagnostic methods, and treatment options, as documented in the existing literature.

2. EVD epidemics from the 1970s to 2013

Table 1 displays a concise overview of epidemic statistics spanning from the 1970s to 2013. Ebola Virus Disease (EVD) initially appeared in 1976 in the Democratic Republic of Congo (DRC) and concurrently in Sudan. Out of the territories affected by the outbreak, 318 cases were documented in the Democratic Republic of Congo (with a case fatality rate of 88%) and 284 cases in Sudan (with a case fatality rate of 53%) [5]. The initial cases of the epidemic were observed in close proximity to the Ebola River in the Democratic Republic of the Congo (DRC). Consequently, the disease was named Ebola hemorrhagic fever (EHF). Two distinct species of the Ebola virus, namely EBOV-Zaire (EBOV-Z) and EBOV-Sudan (EBOV-S), were subsequently identified and confirmed. In 1977, there was a single instance of a death caused by EBOV-Z in Zaire. Following that, EBOV-S resurfaced in Sudan in 1979, resulting in 34 cases, out of which 22 were fatal.

There were no other instances reported until 1994, when a previously unknown species of Ebola virus (EBOV-IC) was identified in a non-fatal case in the Ivory Coast. A verified case was identified who had travelled from Liberia to Sierra Leone and had antibodies to the Ebola virus (EBOV), indicating the presence of EBOV-IC (Ebola virus intercountry transmission) in Liberia[11]. These occurrences indicate that the Ebola virus (EBOV) had expanded its presence from regions in Central Africa to West Africa. In 1995, an outbreak of Ebola Virus Disease (EVD) caused by the Ebola Zaire virus (EBOV-Z) resurfaced in the Democratic Republic of the Congo (DRC)[12]. This significant outbreak resulted in around 315 reported cases and 250 fatalities, with a case fatality rate (CFR) of 81%. The EBOV-Z species demonstrated a significant genetic similarity to the strains isolated in Zaire in 1976[13]. EBOV-S subsequently surfaced in Uganda between 2000 and 2001, leading to approximately 425 reported cases and 224 fatalities (Case Fatality Rate: 53%). The detected EBOV species may be definitively classified as part of the EBOV-S strains that were isolated in Sudan in 1976[1,14,15]. A total of 17 cases and 7 deaths were reported in Yambio County, South Sudan in 2004, resulting in an EBOV-S outbreak with a case fatality rate (CFR) of 41%. The initial instance had slaughtered a primate, and the primary mode of infection among humans was mostly through direct contact[16]. An outbreak of EBOV-Z was reported in the Republic of Congo from 2002 to 2003, resulting in 143 cases, of which 128 were fatal, with a Case Fatality Rate (CFR) of 89%. Another outbreak occurred in the Democratic Republic of Congo (DRC) in 2007, with 264 suspected cases and 187 deaths, resulting in a CFR of 71%. In November 2007, a new strain of the Ebola virus, known as Bundibugyo ebolavirus (EBOV-B), was discovered in Western Uganda. By January 2008, when the outbreak was coming to an end, there had

been 149 suspected cases and 37 deaths reported. During the 2008 Ebola outbreak in the Democratic Republic of the Congo, there were a total of 32 reported cases in Kasai Occidental Province. Out of these cases, 15 resulted in death, resulting in a Case Fatality Rate (CFR) of 47%. In May 2011, a patient who was believed to have EHF died after coming into contact with EBOV-S in Luwero District, Uganda[22]. The next year, an outbreak among 11 patients led to 4 deaths from EHF in Kibaale District[23]. There was another outbreak of Ebola Virus Disease (EVD) in the Democratic Republic of the Congo (DRC).

Table 1: Outbreaks of EVD from 1970s to 2014*.

Year	Outbreak location	Species	Human cases		
			Reported number of human cases	Reported number of deaths among cases	CFR (%)
1976	Democratic Republic of the 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)	Taï Forest	1	0	0
1995	Democratic Republic of the Congo	Zaire	315	250	81
1996 (January-April)	Gabon	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		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	Bundibungyo	149	37	25
November 2008	Philippines	Reston	6	0	0

			(asymptomatic)		
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*	4	36
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 contries	Zaire	15 113*	5 406	36

*: These data are based on earier 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

According to an epidemiological analysis, the first death in the current 2014 outbreak was recorded in Guinea in December 2013, based on laboratory-confirmed cases[4]. The individual in question was a toddler aged 2 years old, and an additional 8 fatalities were verified throughout the period spanning from December 2013 to February 2014 within the confines of Meliandou hamlet, located in Guéckédou Prefecture. The disease may have transmitted from some of these individuals to others in adjacent prefectures such as Macenta, Nzérékoré, and Kissidougou[4]. The prefectures of Guéckédou and Macenta share a border with Liberia and Sierra Leone to the north. The epidemiological research documented 15 laboratory-confirmed cases of Ebola Virus Disease (EVD) that resulted in death[4]. EBOV-Z was shown to be the causal agent, and phylogenetic analysis indicated that a distinct cluster had emerged from the previously reported EBOV strains found in the Democratic Republic of Congo and Gabon.[4].

4. EVD epidemics in West Africa in 2014

The comparatively minor EVD epidemics in Guinea might have extended to neighbouring countries like Liberia and Sierra Leone[26]. As of November 16, 2014, a total of 15,113 cases of Ebola Virus Disease (EVD) have been documented in eight countries since the start of the outbreak. These instances include confirmed, probable, and suspected cases. Out of the total number, there have been 5406 deaths, resulting in a Case Fatality Rate (CFR) of 35.8% [27]. As of November 2014, there have been a total of 1,971 cases of Ebola Virus Disease (EVD) in Guinea, with a Case Fatality Rate (CFR) of 60.4%. In Liberia, there have been 7,069 cases with a CFR of 41.9%, and in Sierra Leone, there have been 6,073 cases with a CFR of 20.6%. Additionally, there have been some reported cases in Mali, Nigeria, and Senegal. There have been four cases of Ebola Virus Disease (EVD) documented in the United States of America and one case in Spain. All of these cases involved either medical staff or individuals who worked in areas affected by the epidemic[27]. Figure 1 displays comprehensive geometric data.

5. Virology of EBOV

EBOV is classified under the Filoviridae family and the Ebolavirus genus[1,10]. There are five recognised species of EBOV: EBOV-Z, EBOV-S, EBOV-IC, EBOV-B, and Reston ebolavirus. The prefix of the surname "filo" is derived from the Latin

term for thread or string. Virions exhibit a variety of morphological structures, including elongated filamentous rods and tightly coiled geometries. These structures have a diameter of around 80 nm and a length ranging from 800 to 14,000 nm [1]. The genome of the Ebola virus (EBOV) is a single-stranded RNA molecule with a negative sense. It has a size of 19 kilobases (Kb). The virions consist of seven proteins, including nucleoprotein, viral proteins 24, 30, 35, and 40, glycoprotein (GP), and L protein. The genome structure is conserved across species, however phylogenetic research has revealed that the species have evolved into distinct lineages with significant genetic divergence (Figure 2). It is worth mentioning that the level of harmfulness of each species might vary significantly from one another[1,3]. For instance, cases of Ebola Virus Disease (EVD) caused by EBOV-Z and EBOV-S have high Case Fatality Rates (CFRs) of over 70% and 50% respectively, but the CFR for EBOV-B is only 27% [3,28]. Reston ebolavirus is believed to exhibit minimal or absent pathogenicity in humans, while it is considered to be highly pathogenic in simians.[1]

6. Ransmission routes

The life cycles of EBOV species are not exactly understood, however it is believed that a certain species of fruit bat serves as the natural hosts (reservoirs) for EBOV[32,33]. Evidence suggests that EBOV can be transmitted from bats to some species of simians[9]. Therefore, bats and simians infected with EBOV may provide an infectious risk to humans if they are handled or consumed[9].
The prevailing belief is that nearly all instances of human-to-human EBOV infections occur as a result of direct exposure to bodily fluids and/or blood (such as saliva, mucus, vomit, faeces, perspiration, tears, breast milk, urine, and semen) from individuals who are symptomatic or deceased[7]. Therefore, it is crucial to exercise utmost caution while dealing with the bodily fluids of patients with Ebola Virus Disease (EVD) in order to prevent infection[7]. Approximately 66% of the Ebola Virus Disease (EVD) cases in the Guinea outbreak of 2014 likely acquired the virus through direct contact with infected bodies during traditional burial rituals in Guinea, either without any protection or with inadequate protection.

7. Clinical features of EVD

EVD often induces the most severe manifestation of viral hemorrhagic fever in human beings. The majority of cases of Ebola Virus Disease (EVD) present with a rapid onset of flu-like symptoms, including high fever, chills, general discomfort, and muscle pain. These symptoms can progress to affect various body systems, leading to gastrointestinal symptoms such as vomiting and diarrhoea, respiratory symptoms such as chest pain and cough, vascular symptoms such as redness and swelling of the eyes, and neurological symptoms such as headache, confusion, and coma. Subsequent to this, there may be the occurrence of hemorrhagic signs such as petechiae, ecchymosis, and uncontrolled mucosal hemorrhage[1,3,6]. These symptoms may bear resemblance to other diseases, such as malaria, cholera, typhoid fever, meningitis, and other viral hemorrhagic fevers. The primary cause of mortality typically stems from the failure of numerous organs, resulting from various complications[1,3,6].
Laboratory results that are not particular to Ebola Virus Disease (EVD) include the

general findings mentioned in references [1,3,35]. During the initial stage of the disease, a decrease in the number of white blood cells (leukocytopenia) and a decrease in the number of lymphocytes (lymphocytopenia) may be observed in the peripheral blood. This is followed by an increase in the number of neutrophils (neutrophilia) and a decrease in the number of platelets (thrombocytopenia) which are commonly observed. Furthermore, it is typical to observe an increase in the levels of ectopic enzymes, such as aspartate transaminase and alanine aminotransferase [1,3]. Irregularities can arise in the blood clotting process, leading to extended prothrombin and partial thrombin time. Pneumonia, a type of secondary bacterial infection, may develop during the last stage[1,3]. Nonfatal instances of the illness may experience a prolonged period of high fever lasting approximately 5 to 9 days. However, symptoms typically start to recover around 7 to 10 days after the illness begins[1,3,36]. During such period, there may be an observable humoral antibody response.

Early-stage Ebola Virus Disease (EVD) does not exhibit any distinct symptoms, making it crucial to obtain laboratory confirmation[1]. RT-PCR and/or immunological approaches, such as ELISA, are commonly employed for detection, similar to other viral infections. [1].

8. Present status of therapeutic drug developments for EVD

Currently, there are no officially sanctioned, conclusive treatments available for EVD, such as vaccinations or antiviral medications[3,34]. Consequently, the primary approach for treating symptoms involves administering electrolyte infusions and/or antibiotics[1,3]. So far, two potential vaccines for Ebola Virus Disease (EVD) have been documented. A prospective EVD vaccine, cAd3-ZEBOV[37], has been developed by the US National Institute of Allergy and Infectious Diseases and GlaxoSmithKline. The vaccine is an adenovirus vector developed from chimpanzees, with an inserted gene from the Ebola virus. The second candidate, rVSV-ZEBOV, was created by the Public Health Agency of Canada in Winnipeg[38]. We are anxiously anticipating the availability of these medications for clinical use.

ZMapp, an investigational medication, has been delivered in three instances to date. The composition consists of three monoclonal antibodies (mAbs) specifically engineered to counteract the effects of EBOV[39]. The monoclonal antibody cocktail specifically attaches to and inactivates the GP protein of the Ebola virus (EBOV), as demonstrated by its ability to prevent infection in monkeys[39]. ZMapp was delivered to two American EVD patients who contracted the virus while providing medical care to EVD patients in Liberia during the current epidemic[40]. Both patients fully recovered from severe EVD. However, a Spanish patient who received the same medicine has unfortunately passed away[40]. The efficacy of this experimental treatment cannot be determined at this early stage.

Favipiravir, a nucleic acid analogue, is being developed as a potential anti-viral medication for the treatment of EVD[41]. This medication was initially created to treat influenza[41,42] and it works by blocking the production of viral RNA through the activity of influenza virus's RNA-dependent RNA polymerase (RdRp)[42]. Given the similarity in many

pathways of viral RNA synthesis between EBOV and influenza viruses[43], it is anticipated that the medication will have comparable effects on the RNA synthesis of EBOV. Studies have shown notable efficacy against Ebola Virus Disease (EVD) in mice[43]. Therefore, it is possible that favipiravir will be tested in clinical trials during the current Ebola Virus Disease (EVD) pandemic.

9. Conclusion

We have summarised the existing understanding of EVD by doing a comprehensive analysis of the available literature. Based on our current understanding, it seems challenging to forecast the magnitude and consequences of future EVD outbreaks. Approximately three decades ago, the human immunodeficiency virus (HIV) infection developed abruptly and rapidly disseminated worldwide. Presently, due to persistent endeavours of the medical community, efficient treatment approaches for HIV infection are accessible. However, complete eradication of the disease has not yet been achieved. Currently, our understanding of EBOV and EVD is limited. However, there is optimism that we may soon discover effective treatment strategies to fight against EVD.

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