HORROR OF EBOLA HAEMORRAGE FEVER: A REVIEW

Mohan Lal¹*, Pawankumar Rai², Ankit Ramawat³, Sirsat Dattatrya⁴ and Afroj Shaikh⁴

¹Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Matunga, Mumbai-400019, India.
²Department of food, Drug & Chemical Toxicology, CSIR-Indian Institute of Toxicology Research, Lucknow - 226 001 Uttar Pradesh, India.
³Department of Pharmaceutical Sciences and Technology, Lachoo Memorial College of Science and Technology, Jodhpur, Rajasthan-342005, India.

ABSTRACT

Ebola virus disease is an acute viral hemorrhagic syndrome marked by fever, systemic hemorrhage, and high mortality. It affects humans and monkeys and has appeared in epidemic form in West Africa and Germany. Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever, is a serious, often fatal disorder in humans. Ebola virus (EBOV) is spread through contact with blood or body fluids of a person who contacted or died from EVD, infected objects like needles and infected animals or bush meat. The EVD is a very serious health problem causing major deaths within a short period duration. As there are no specific treatment or vaccines available, prevention is the only option to control the spread of disease. The object of present study is to provide in depth knowledge about the clinical aspects of Ebola hemorrhagic fever.

INTRODUCTION

Viral haemorrhagic fever (VHF) is a group of systemic mild to life-threatening viral infection often complex by haemorrhagic syndromes. The most involved with VHFs include Ebola, Marburg, Lassa, and Crimean-Congo haemorrhagic fever viruses because of known secondary human-to-human transmission.

Ebola virus disease (EVD) is bringing about by infection with Ebola virus which is a part of the family called Filoviridae. EVD in humans has a case the ability to cause such death rate to
ninety percent. Since the first report of the EVD sudden happens in West Africa in March 2014, the aggregate numbers of cases attributed to EVD are together becoming larger, making this EVD outbreak the most extensive ever recorded in terms of geographical spread and overall number of cases and end of life stated.[1,2]

EVD is communicated to human through touch with secretions, blood, organs and other body fluids of pullulated animals including chimpanzees, gorillas, fruit bats, monkeys, forest antelopes and porcupines. Human-to-human communicated is possible through direct touch with blood, secretions, organs or other body fluids of infected people, and indirect touch with environments contaminated with such fluids.[2,3] Healthcare workers have repeatedly been contaminated through close contact with patients when contamination control standard are not strictly practiced. The risk for person-to-person communicated of Ebola virus is topmost during the latter stages of illness, when vomiting, diarrhoea and haemorrhage may lead to splash and droplet generation.[4] This interim advice on infection control of EVD in healthcare settings is prepared in light of the latest situation. This advice will be updated accordingly when there is revising on the scientific evidence on the virus and linked infections.[5,6]

Ebola Virus Disease is a complex zoonosis that is highly pathogenic in humans. Ebola hemorrhagic fever (EHF) is a severe, often-highly mortal disease in humans and non-human primates (monkeys, gorillas, and chimpanzees) that has appeared occasionally since its initial understanding in 1976. The disease is beginning by infection with Ebola virus, named after Ebola River in the Democratic Republic of the Congo (formerly Zaire) in Africa, where it was first identified. The virus is one of two-members of a family of RNA viruses called the Filoviridae. There are four identified sub-types of Ebola virus. Three of the four have pathogenic disease in humans: Ebola- Zaire, Ebola- Sudan, and Ebola-Ivory Coast. The fourth, Ebola-Reston, has begun disease in non-human primates, but not in humans. EHF often arrives in sporadic outbreaks coinciding with the rainy season, and is usually spread in humans within a health-care setting.[7,8]

The natural reservoir host of Ebola Viruses remains unknown. However, on the basis of evidence and the nature of similar viruses, researchers believe that the virus is animal born and that bats are the most likely reservoir. Four of the five subtypes occur in an animal host native to West Africa. A Similar host, most likely in the Philippines, is probably identified with the Ebola- Reston subtype, which was isolated from cynomologous monkeys that were
exotic to the United States and Italy from the Philippines. The virus is not known to be original to the other continents, such as North America. The name of this disease was borrowed from the Ebola river which is near to the Yambuku village where the first crash of the disease was identified in the year 1976. According to the World Health Organization (WHO), a total of 24 crash involving 1,716 cases of ebola have been described between 1976 and 2013. The largest crash is the tropical regions of sub-Saharan Africa and Western Africa centered in Guinea, Sierra Leone and Liberia where ebola is seriously a widespread occurrence of an infectious disease in a community at a particular time. As of 12 th March 2015, a total of 24,544 cases have been described which resulted in 10,111 deaths.[9,10]

History

In 1976 the first identified case of Ebola was on 26 August 1976, in Yambuku, a small Rural Village in Mongala District in northern Democratic Republic of the Congo (then known as Zaire). The first victim, and the indicator case for the disease, was village school headmaster Mabalo Lokela, who had travel an area nearby the Central African Republic border along the Ebola river between 12–22 August.[11]

On 8 September 1976 he died of what would become known as the Ebola virus species of the Ebola virus. Subsequently a number of other cases were described, almost all centered on the Yambuku mission hospital or having close contact with another case. A total 318 cases and 280 deaths, an 88% mortality rate showed in the DRC. The Ebola crash was contained with the help of the WHO and transport from the Congolese air force, by quarantining villagers, sterilizing medical equipment, and providing protective clothing. The virus responsible for the initial crash first thought to be Marburg virus was later single-out as a new type of virus relevant to Marburg, and named after the nearby Ebola river. Another ebola-virus, the Sudan virus species, was also found that same year when crashes arise in Sudan, affecting 284 people and killing 151.[1,8,12]
Table 1: Historical chronology of Ebola virus crashes (CDC 2014,2016).[13]

<table>
<thead>
<tr>
<th>Crashes year</th>
<th>Country</th>
<th>No. of cases</th>
<th>Mortality ratio</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>Zaire (Democratic Republic of the Congo)</td>
<td>318</td>
<td>280 (88%)</td>
<td>[8,14]</td>
</tr>
<tr>
<td>1977</td>
<td>Zaire</td>
<td>1</td>
<td>1 (100%)</td>
<td>[1,15]</td>
</tr>
<tr>
<td>1994</td>
<td>Gabon</td>
<td>52</td>
<td>31 (60%)</td>
<td>[16]</td>
</tr>
<tr>
<td>1995</td>
<td>Democratic Republic of the Congo</td>
<td>315</td>
<td>250 (81%)</td>
<td>[17]</td>
</tr>
<tr>
<td>1996</td>
<td>Russia</td>
<td>1</td>
<td>1 (100%)</td>
<td>[11]</td>
</tr>
<tr>
<td>1996</td>
<td>South Africa</td>
<td>2</td>
<td>1 (50%)</td>
<td>[10]</td>
</tr>
<tr>
<td>1996–1997 (July–Jan)</td>
<td>Gabon</td>
<td>60</td>
<td>45 (74%)</td>
<td>[17]</td>
</tr>
<tr>
<td>1996 (January–April)</td>
<td>Gabon</td>
<td>37</td>
<td>21 (57%)</td>
<td>[18]</td>
</tr>
<tr>
<td>October 2001–March 2002</td>
<td>Republic of the Congo</td>
<td>57</td>
<td>43 (75%)</td>
<td>[19,20]</td>
</tr>
<tr>
<td>October 2001–March 2002</td>
<td>Gabon</td>
<td>65</td>
<td>53 (82%)</td>
<td>[21]</td>
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<tr>
<td>December 2002–April 2003</td>
<td>Republic of the Congo</td>
<td>143</td>
<td>128 (89%)</td>
<td>[22]</td>
</tr>
<tr>
<td>Nov. 2003</td>
<td>Republic of the Congo</td>
<td>35</td>
<td>29 (83%)</td>
<td>[20]</td>
</tr>
<tr>
<td>2004</td>
<td>Russia</td>
<td>1</td>
<td>1 (100%)</td>
<td>[23]</td>
</tr>
<tr>
<td>2007</td>
<td>Democratic Republic of the Congo</td>
<td>264</td>
<td>187 (71%)</td>
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<tr>
<td>August–November 2014</td>
<td>Democratic Republic of the Congo</td>
<td>66</td>
<td>49 (74%)</td>
<td>[24]</td>
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<tr>
<td>(Dec) 2013–2016</td>
<td>Guinea, Sierra Leone, Liberia</td>
<td>28,652</td>
<td>11,325 (39%)</td>
<td>[25]</td>
</tr>
<tr>
<td>2014</td>
<td>Uganda</td>
<td>1(^b)</td>
<td>1 (100%)</td>
<td>[4]</td>
</tr>
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<td>Republic of the Congo</td>
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The second major crash arise in 1995 in the Democratic Republic of Congo, affecting 315 and killing 254. The next big crash arise in Uganda in 2000, affecting 425 and killing 224; in this case the Sudan virus was found to be the Ebola virus species subject for the outbreak. In 2003 there was a crash in the Republic of Congo that affected 143 and killed 128, a mortality rate of 90%, the highest to date.[28]
In August 2007, 103 people were affected by a suspected hemorrhagic fever crash in the village of Kampungu, Democratic Republic of the Congo. The crash initiated after the funerals of two village chiefs, and 217 people in four villages fell ill. The 2007 crash eventually affected 264 individuals and resulted in the deaths of 187.[26] On 30 November 2007, the Uganda Ministry of Health confirmed a crash of Ebola in the Bundibugyo District in Western Uganda. After evidence of samples tested by the United States National Reference Laboratories and the Centers for Disease Control, the WHO accepted the presence of a new species of Ebola virus, which was provisionally named Bundibugyo. The WHO noted 149 cases of this new strain and 37 of those led to deaths. The WHO confirmed two small crashes in Uganda in 2012. The first crash affected 7 people and resulted in the death of 4 and the second affected 24, resulting in the death of 17. The Sudan variant was responsible for both outbreaks. On 17 August 2012, the Ministry of Health of the Democratic Republic of the Congo noted an outbreak of the Ebola-Bundibugyo variant in the eastern region. Other than its discovery in 2007, this was the only time that this variant has been finding as the Ebola virus responsible for an outbreak. The WHO revealed that the virus had afflicted 57 people and claimed 29 lives. The probable cause of the crash was infected bush meat hunted by local villagers around the towns of Isiro and Viadana.[18, 29]

In March 2014, the WHO reported a major Ebola outbreak in Guinea, a western African nation; it is the largest ever documented, and the first documented in the region. Researchers indicated the crash to a two-year old child who died on 6 December 2013. On 8 August 2014, the WHO stated the epidemic to be an international public health emergency. Urging the world to offer aid to the affected regions, the Director-General said, "Countries affected to date simply do not have the capacity to regulate an outbreak of this magnitude and complication on their own. I urge the international community to implement this support on the most crucial basis possible. By mid-August 2014, Doctors without Borders noted the situation in Liberia's capital Monrovia as "catastrophic" and "deteriorating daily".[30]

They report that fears of Ebola among staff members and patients have shut down much of the city’s health system which has risen in leaving many people without cure for other conditions. By late August 2014, the disease had spread to Nigeria. By 6 September 2014, 4,293 suspected cases including 2,296 deaths had been reported, however the World Health Organization has said that these numbers may be vastly miscalculated. Additionally the crash has resulted in more than 120 healthcare employee deaths partly due to the lack of equipment
and long hours. On 8 September 2014, WHO warned the number of new cases in Liberia was rising exponentially, and would rise by "many thousands" in the following 3 weeks. Separately from the human cost, the crash has seriously destroyed the economies of the affected countries.

In August 2014, attempts to contain the outbreak were enacted by placing troops on roads to cordon off the infected areas and stop those who may be infected from leaving and further spreading the virus. By September, with the closure of borders, the cancellation of airline flights, the evacuation of foreign workers and a collapse of cross-border trade, the national deficits of Guinea, Sierra Leone and Liberia were widening to the point where the IMF was considering expanding its financial support to the 3 countries. The WHO, Médecins sans Frontières, and UN health care workers have all critized the travel restrictions saying they are not justified and are potentially worsening the crisis. A Financial Times report suggested the economic impact of the outbreak could kill more people than the virus itself.\[31\]

The last known strain of Ebola, Ebola Cote d'Ivoire (EBO-CI) was found in 1994 when a female ethologist operating a necropsy on a dead chimpanzee from the Tai Forest. Snuffing out the lives of almost 80% of population that undergo from disease, Ebola is definitely a fever condition that has a capability to affect millions. The first outbreak of Ebola virus was in 2014 in India.\[14,32\]

**Overview of Virus**

Filoviruses are helical, non-segmented, negative, single-stranded RNA (SS-RNA) viruses, polymorphic, non-infectious, and have variable lengths. Infectious Ebola virions are usually
920 nm in length, 80 nm in diameter, and have a membrane stolen from the host cell by budding. The virus encodes for a nucleoprotein, a glycoprotein, 7 polypeptides, a polymerase, and 4 other undesignated proteins. These proteins are made from polyadenylated mRNA transcribed in the host cell from the virus RNA.\cite{21,33}

![Figure 2: Representation of Virion of Ebola virus.](image)

The family Filoviridae consists of two genera, the Ebola and Marburg viruses, which are among the most virulent pathogens in humans. Ebola virus is a nonsegmented, negative sense, single stranded RNA virus that resembles rhabdo viruses and paramyxoviruses in its genome organization and duplication mechanisms. It is a member of the family Filoviridae, taken from the Latin "filum," meaning thread like, based upon their filamentous structure. In the past, Ebola and Marburg viruses were classified as "hemorrhagic fever viruses", based upon their clinical symptoms, which include coagulation defects, bleeding, and shock. The genus Ebola virus is divided into five species (Zaire, Sudan, Ivory Coast, Bundibugyo, and Reston). The following four species cause disease in humans.\cite{34}

- The Zaire virus, since it was first identified in 1976, has caused multiple large crash in Central Africa, with mortality rates of 55 to 88 percent. It is the causative agent of the 2014 West African epidemic.
- The Sudan virus has been associated with a case mortality rate of approximately 50 percent in four epidemics: two in Sudan in the 1970s, one in Uganda in 2000, and another in Sudan in 2004.
- The Ivory Coast virus has only been identified as the cause of illness in one person, and that individual survived. The exposure occurred when an ethologist performed a necropsy
on a chimpanzee found dead in the Tai Forest, where marked reductions in the great ape population had been observed.

- The Bundibugyo virus emerged in Uganda in 2007, causing an outbreak of Ebola virus disease with a lower case fatality rate (approximately 30%) than is typical for the Zaire and Sudan viruses. Sequencing has shown that the agent is most closely related to the Ivory Coast species. The fifth Ebola species, the Reston virus, differs markedly from the others, because it is apparently maintained in an animal reservoir in the Philippines and has not been found in Africa.\[26]\n
The Ebola Reston virus was found when it caused an outbreak of fatal infection in macaques foreign into the United States in 1989. This episode brought the filoviruses to worldwide attention through the publication of Richard Preston's book, The Hot Zone. Three more crash occurred among non-human primates in detection facilities in the United States and Europe before the Philippine animal supplier terminates operations. None of the personnel who were discovered to sick animals without protective equipment became ill, but several animal caretakers showed evidence of sero-conversion. Nothing further was heard of Reston virus until 2008, when the inquiry of a crash of disease in pigs in the Philippines suddenly reported that some of the sick animals were affected both by an arterivirus (porcine reproductive and respiratory disease virus) and by Ebola Reston virus. Serologic studies have shown that a small percentage of Philippine pig farmers have IgG-antibodies against the agent without ever establish severe symptoms, providing additional data that Ebola Reston virus is able to cause mild or asymptomatic infection in humans. Whether or not the virus recovered from Philippine pigs and Philippine macaques is the same is unknown.\[2]\n
Transmision

- The Ebola virus is spread by direct contact with the blood, secretions, organs or other body fluids of infected persons.
- Burial ceremonies where mourners have direct contact with the body of the diseased person can play a significant role in the communication of Ebola.
- The infection of human cases with Ebola virus through the handling of infected chimpanzees, gorillas, and forest antelopes both dead and alive has been noted in Côte d'Ivoire, the Republic of Congo and Gabon. The communication of the Ebola Reston strain through the conducting of cynomologous monkeys has also been noted.\[28]\n- Health care employees have often been infected while treating Ebola patients, through
close contact without correct infection control precautions and adequate barrier nursing procedures.

- The virus has been proved to be transmitted through body fluids. Transmission through oral exposure and through conjunctiva exposure is likely, which have been confirmed in non-human primates.
- Filoviruses are not naturally transmitted by aerosol. They are, however, highly infectious as breathable 0.8-1.2 micron droplets in laboratory conditions.¹

Pathogenesis

After infection, the victims experience an early period of rapid viral multiplication which, in lethal cases, is accompanied by an ineffective immune response. Although a full understanding of Ebola virus disease demands further investigations, some aspects of pathogenesis have been partly elucidated.³⁵

- sGP, the secretory glycoprotein mentioned above, is produced in large quantities during the initial phase of Ebola virus infection. sGP prevents the appearance of an early and effective immune response through inhibition of neutrophil activation and production of profound lymphopenia.
- The virus invades, replicates in and destroys the endothelial cells of the patient. This leads to disseminated intravascular coagulation (DIC) which largely contributes to the hemorrhagic manifestations so characteristic of many but not all Ebola infections.
- Ebola virus infection is characterized by rapid and extensive viral replication in all tissues resulting in widespread focal necrosis, most severe in liver but also seen in spleen, lymph nodes, kidneys, lungs and gonads.
- Host tissues and body fluids including semen and blood contain huge quantities of virus particles and are highly infectious.³⁵,³⁶

Several animal models have been developed to study the pathogenesis of Ebola virus infection and to assess the efficacy of various vaccine approaches. Guinea pigs and nonhuman primates represent the primary animal models for vaccine development because the progression and pathogenesis most closely resemble those of the human disease. A murine model was later developed by serial passage of virus in mice. Though the model allows the use of knockout and inbred strains to evaluate genetic determinants of disease, it is considered less predictive of human disease because it relies on a serially passaged, attenuated virus. While symptoms and time course of disease in guinea pigs parallel those in
humans, nonhuman primate infection is considered the most predictive and useful for vaccine development.\textsuperscript{[37]}

Live attenuated viruses and recombinant proteins have been used successfully in a variety of vaccines, but the safety and immunogenicity of gene-based vaccines have proven increasingly attractive. Among the gene-based approaches, naked plasmid DNA has been used successfully in animal models to direct the synthesis of immunogens within the host cells and has proven helpful in a variety of infectious diseases.\textsuperscript{[9]}

**Sign & Symptoms**

Symptoms may appear from 2 to 21 days after exposure to Ebola. The symptoms include fever, severe headache, muscle pain, weakness, fatigue, diarrhoea, vomiting, abdominal pain, unexplained hemorrhage.\textsuperscript{[38]}

EVD is a rare but severe and often deadly disease. Recovery from EVD depends on good supportive clinical care and the patient’s immune response. Studies show that survivors of Ebola virus infection have antibodies (molecules that are made by the immune system to label invading pathogens for destruction) that can be detected in the blood up to 10 years after recovery.\textsuperscript{[31]}

![Symptoms of Ebola](image)

**Figure 2: Symptoms of Ebola.**\textsuperscript{[31]}
Diagnosis

Laboratory Diagnosis
Routine laboratory findings are characterized by thrombocytopenia, leucopenia and lymphopenia followed by neutropenia. ALT and AST may be elevated. Later blood urea nitrogen and serum creatinine increase. Terminally ill patients may develop a metabolic acidosis that may explain the frequent occurrence of tachypnea as an attempt for compensatory hyperventilation.[12]

Definitive Diagnosis
The modalities available for definitive diagnosis include
- RT-PCR: presently the method of choice. It takes 3-10 days to become positive after the display of symptoms.
- Virus isolation in Vero cells – a highly dangerous procedure which can be undertaken only in a few selected high containment laboratories in the world.
- Antigen detection by enzyme-linked immunosorbent assay (ELISA).
- Detection of IgG and IgM-antibodies by ELISA – the display of these antibodies may be slowed.[39]

Treatment
Treatment options for patients infected with Ebola virus are defined. Supportive therapy is centered on fluid resuscitation, electrolyte imbalance correction, treating complicating infections and preventing problems of shock. Experimental therapies like ZMapp, brincidofovir, TKM-Ebola and favipiravir were used during the recent crash. Several medications such as amiodarone, chloroquine and clomiphene may prevent the transmission of or treat Ebola virus. Different vaccine therapies are also in early-stage development. One of the vaccine strategies using recombinant vesicular stomatitis virus as a delivery vector has demonstrated efficacy when used for pre-exposure and post-exposure prophylaxis. Close supervision and care by healthcare professionals is very important for this infection. A patient with Ebola virus disease may need intensive care unit (ICU) services.[40]

Recent advances in understanding the pathogenesis of Ebola virus invasion of host cells especially that of humans exposed that the virus hijacks the cholesterol transporter protein, NPC1 to infect host cells. As the absence of these cells will lead to dementia, more research is compulsory before administration of NPC1 blocking drugs.[41]
Ayurvedic Approach
Ayurveda though being an age-old life science clearly mention’s about such disease conditions. A specific chapter on Janapadodhwans in Charak Samhita Vimansthan 3rd Adhyay explains epidemic disease and its causing factors. In Sushrut samhita Kushthanidanaadhyay there is a detail on mechanism of transfer of disease. They are called Aupasargik rogas (Comunicable diseases). From these references we come to know that in age-ago time also there were such epidemics. A detailed regimen for such diseases is also depicted in Charak Samhita as use of Panchakarma and Rasayana along with Sadvrittapalan.\textsuperscript{5}

CONCLUSION
In conclusion, Ebola virus is the serious threat for human or primates, in the form of infection or Bio-terrorism agent. The Ebola virus is spread by direct contact with the blood, body fluids and tissues of infected persons. Transmission of the Ebola virus has also occurred by handling sick or dead infected wild animals (chimpanzees, gorillas, monkeys, forest antelope, fruit bats). The review is aimed at Ebola hemorrhagic fever, its sign, symptoms, diagnosis, mode of transmission, prognosis as well as treatment. The complaint of Ebola hemorrhagic fever is common but presents a challenging diagnostic exercise. Attempt is made in above review article to enumerate various clinical aspects of Ebola hemorrhagic fever. The understanding of EBOV pathogenesis is crucial for the development of efficacious treatments and vaccines. Targeted therapy and vaccination are an immediate and highest priority.

REFERENCES


