Journal of Pharma Research
Available online through
www.jprinfo.com

Review Article
ISSN: 2319-5622

EBOLA VIRUS DISEASE: A REVIEW

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Received on: 04-05-2016; Revised and Accepted on: 16-05-2016

ABSTRACT

Ebola virus disease is an acute viral syndrome marked by fever, systemic hemorrhage, and high mortality; it affects humans and monkeys and has appeared in epidemic form in Africa and Germany. Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever, is a severe, often fatal illness in humans. Ebola virus (EBOV) is transmitted through contact with blood or body fluids of a person who contracted or died from EVD, contaminated objects like needles and infected animals or bush meat. Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever, is a severe, often fatal illness in humans. Ebola virus (EBOV) is transmitted through contact with blood or body fluids of a person who contracted or died from EVD, contaminated objects like needles and infected animals or bush meat. The Ebola virus disease is a very serious health problem causing major deaths within a short period. 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.

Key Words: *Ebola Virus Disease, Transmission, Pathogenesis, Treatment.*

INTRODUCTION

Ebola Virus Disease is a complex zoonosis that is highly virulent in humans. It is also known as Ebola Hemorrhagic Fever. Ebola hemorrhagic fever (EHF) is a severe, often-fatal disease in humans and nonhuman primates (monkeys, gorillas, and chimpanzees) that has appeared sporadically since its initial recognition in 1976. The disease is caused by infection with Ebola virus, named after a river in the Democratic Republic of the Congo (formerly Zaire) in Africa, where it was first recognized. The virus is one of two members of a family of RNA viruses called the Filoviridae. There are four identified subtypes of Ebola virus. Three of the four have caused disease in humans: Ebola- Zaire, Ebola-Sudan, and Ebola-Ivory Coast. The fourth, Ebola-Reston, has caused disease in non human primates, but not in humans. EHF typically appears in sporadic outbreaks coinciding with the rainy season, and is usually spread in humans within a health-care setting [1, 2]. 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 Africa. A Similar host, most likely in the Philippines, is probably associated with the Ebola- Reston subtype, which was isolated from cynomologous monkeys that were imported to the United States and Italy from the Philippines. The virus is not known to be native to the other continents, such as North America. The name of this disease was derived from the *Ebola* river which is near to the *Yambuku* village where the first outbreak of the disease was identified in the year 1976. According to the World Health Organization, a total of 24 outbreaks involving 1,716 cases of ebola have been reported between 1976 and 2013. The largest outbreaks are the tropical regions of sub-Saharan Africa and Western Africa centered in Guinea, Sierra Leone and Liberia where ebola is seriously epidemic. As of 12 March 2015, a total of 24,544 cases have been reported which resulted in 10,111 deaths [3-7].

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 index case for the disease, was village school headmaster Mabalo Lokela, who had toured an area near the Central African Republic border along the Ebola river between 12–22 August. On 8 September he died of what would become known as the Ebola virus species of the Ebola virus. Subsequently a number of other cases were reported, almost all centered on the Yambuku mission hospital or having close contact with another case. 318 cases and 280 deaths (an 88% fatality rate) occurred in the DRC. The Ebola outbreak was contained with the help of the World Health Organization and transport from the Congolese air force, by quarantining villagers, sterilizing medical equipment, and providing protective clothing. The virus responsible for the initial outbreak, first thought to be Marburg virus was later identified as a new type of virus related to Marburg, and named after the nearby Ebola river. Another ebolavirus, the Sudan virus species, was also identified that same year when an outbreak occurred in Sudan, affecting 284 people and killing 151 [8, 9].

The second major outbreak occurred in 1995 in the Democratic Republic of Congo, affecting 315 and killing 254. The next major outbreak occurred in Uganda in 2000, affecting 425 and killing 224; in this case the Sudan virus was found to be the Ebola virus species responsible for the outbreak. In 2003 there was an outbreak in the Republic of Congo that affected 143 and killed 128, a death rate of 90%, the highest to date.

In August 2007, 103 people were infected by a suspected hemorrhagic fever outbreak in the village of Kampungu, Democratic Republic of the Congo. The outbreak started after the funerals of two village chiefs, and 217 people in four villages fell ill. The 2007 outbreak eventually affected 264 individuals and resulted in the deaths of 187. On 30 November 2007, the Uganda Ministry of Health confirmed an outbreak of Ebola in the Bundibugyo District in Western Uganda. After confirmation of samples tested by the United States National Reference Laboratories and the Centers for Disease Control, the World Health Organization confirmed the presence of a new species of Ebola virus, which was tentatively named Bundibugyo. The WHO reported 149 cases of this new strain and 37 of those led to deaths. The WHO confirmed two small outbreaks in Uganda in 2012. The first outbreak 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 reported 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 identified as the Ebola virus responsible for an outbreak. The WHO revealed that the virus had sickened 57 people and claimed 29 lives. The probable cause of the

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outbreak was tainted bush meat hunted by local villagers around the towns of Isiro and Viadana [10, 11].

In March 2014, the World Health Organization (WHO) reported a major Ebola outbreak in Guinea, a western African nation; it is the largest ever documented, and the first recorded in the region. Researchers traced the outbreak to a two-year old child who died on 6 December 2013. On 8 August 2014, the WHO declared 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 manage an outbreak of this size and complexity on their own. I urge the international community to provide this support on the most urgent basis possible. By mid-August 2014, Doctors without Borders reported the situation in Liberia's capital Monrovia as "catastrophic" and "deteriorating daily". They report that fears of Ebola among staff members and patients have shut down much of the city's health system which has resulted in leaving many people without treatment 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 underestimated. Additionally the outbreak has resulted in more than 120 healthcare worker 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 increasing exponentially, and would increase by "many thousands" in the following 3 weeks. Aside from the human cost, the outbreak has severely eroded 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 [12].

The last known strain of Ebola, Ebola Cote d'Ivoire (EBO-CI) was discovered in 1994 when a female ethologist performing a necropsy on a dead chimpanzee from the Tai Forest. Snuffing out the lives of almost 80% of population that suffers 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 [13, 14].

Overview of Virus:

Filoviruses are helical, non-segmented, negative, single-stranded RNA viruses, polymorphic, noninfectious, 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 [15].

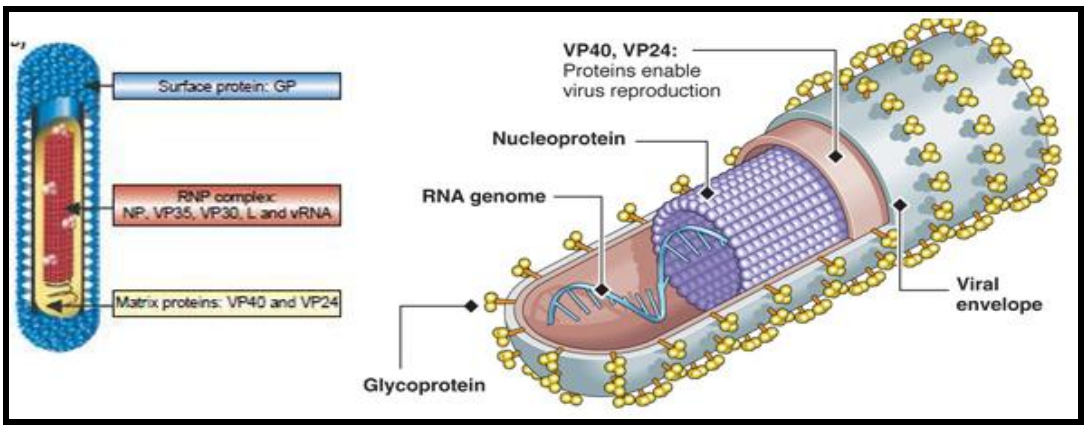

Fig. 1: General Structure of Ebola Virus

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 replication 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 manifestations, 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.

- The Zaire virus, since it was first recognized in 1976, has caused multiple large outbreaks 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 fatality 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.

The Ebola Reston virus was discovered when it caused an outbreak of lethal infection in macaques imported 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 outbreaks occurred among nonhuman primates in quarantine facilities in the United States and Europe before the Philippine animal supplier ceased operations. None of the personnel who were exposed to sick animals without protective equipment became ill, but several animal caretakers showed evidence of seroconversion. Nothing further was heard of Reston virus until 2008, when the investigation of an outbreak of disease in pigs in the Philippines unexpectedly revealed that some of the sick animals were infected 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 developing severe symptoms, providing additional evidence 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 [16].

Transmission:

- The Ebola virus is transmitted 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 transmission 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 documented in Côte d'Ivoire, the Republic of Congo and Gabon. The transmission of the Ebola Reston strain through the handling of cynomologous monkeys has also been reported [17].
- Health care workers have frequently been infected while treating Ebola patients, through close contact without correct infection control precautions and adequate barrier nursing procedures.
- The virus has been confirmed 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 [18].

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.

- 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 [19].

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 [20].

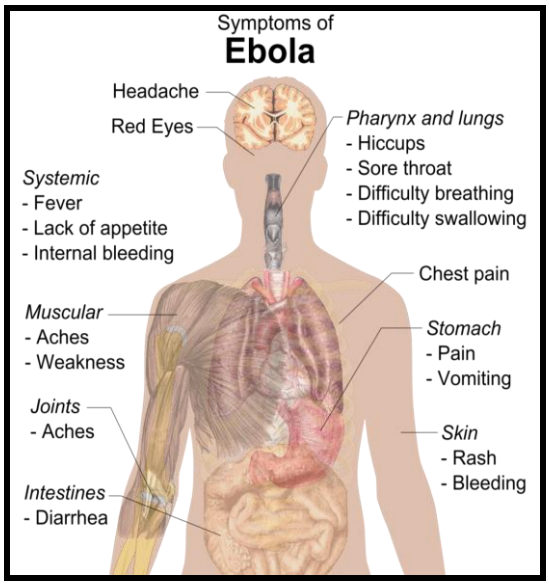

Fig. 2: Symptoms of Ebola

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.

Definitive Diagnosis:

The modalities available for definitive diagnosis include:

- RT-PCR: Currently the method of choice. It takes 3-10 days to become positive after the appearance of symptoms.
- Virus isolation in Vero cells – an extremely dangerous procedure which can be undertaken only in a few selected high containment laboratories in the world.
- Antigen detection by ELISA.
- Detection of IgG and IgM antibodies by ELISA – the appearance of these antibodies may be delayed [19].

Treatment:

Treatment options for patients infected with Ebola virus are limited. Supportive therapy is centered on fluid resuscitation, electrolyte imbalance correction, treating complicating infections and preventing complications of shock. Experimental therapies like ZMapp, brincidofovir, TKM-Ebola and favipiravir were used during the recent outbreak. 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-xposure 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.

Recent advances in understanding the pathogenesis of Ebola virus invasion of host cells especially that of humans revealed that the virus hijacks the cholesterol transporter protein, NPC1 to invade host cells. As the absence of these cells will lead to dementia, more research is required before administration of NPC1 blocking drugs [21].

Ayurvedic Approach:

Ayurveda though being an ancient life science clearly mention's about such disease conditions. A detailed chapter on *Janapadodhwans* in *Charak Samhita Vimansthan* 3rd Adhyay explains epidemic disease and its etiological factors. In *Sushrut samhita Kushthanidan*adhyay there is a good description on mode of transfer of disease. They are called *Aupasargik rogas* (Comunicable

diseases). From these references we come to know that in ancient time also there were such epidemics. A detailed regimen for such diseases is also described in Charak Samhita as use of *Panchakarma* and *Rasayana* along with *Sadvrittapalan* [22].

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 transmitted 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 s 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.

ACKNOWLEDGMENT

The people, who contributed generously their time and insights to this project, we gratefully acknowledgement them. We would like to thank and express our gratitude to our honorable Chairman Mr. Ashok Sharma & Respected Principal Dr. Parshuram Rai for providing facilities to complete review work.

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How to cite this article:

Praveen Kumar et al., EBOLA VIRUS DISEASE: A REVIEW, J. Pharm. Res., 2016; 5(5): 104-107.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil