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Ebola Virus Disease: A Brief Review

T.Mangilal*[1], Ajmera Shanti Priya1,Kalyani Jatoth [2], M. Satish Kumar [3], L.Thirupathi [3], P. Veeresh Kumar [4]

**1 Department of pharmacy, UCT, OU, Hyderabad, Telangana, India.*
1 Department of Microbiology, Kakatiya University, Warangal, T.S, India.
2Department of Microbiology, Pingle College of Science, Kakatiya University, Warangal, T.S, India.
3GeethanjaliCollege of Pharmacy, Cheeryal, RangareddyDistrict,T.S, India.
4 JPNES Group of Institutions, Faculty of Pharmacy, Mahabubnagar, T.S, India..
*E-mail: teelavath@gmail.com

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Abstract

Ebola virus disease (EVD) is one of the most life-threatening viral disease to mankind with high fatality rate (up to 90%). In 1970, the first EVD outbreak was appeared in the Democratic Republic of the Congo. Since 30 years, several outbreaks were reported in the central region of Africa that include Sudan, Zaire and Uganda. Ebola hemorrhagic fever (EHF) is a deadly disease of animal can also be transmitted to human and non-human primates. Ebola virus belongs to the family, *Filoviridae* and also has five genetically distinct species such as *Sudan ebolavirus, Zaire ebolavirus, Bundibugyo ebolaviru, Côte d'Ivoire ebolavirus* and *Reston ebolavirus*. The virulence of Ebola virus involved in several immunoevasion mechanisms that include an inhibition of type I interferon responsible for innate immunity, epitope masking, etc. The incubation period of ebola virus is less than 3 weeks. Ebola virus infection can cause a systemic inflammatory response and immune suppression finally that leads to multiple organ failure and shock due to the damage of the immune systems, coagulation and vascular systems caused by unrestricted replication of ebola virus. There is no appropriate antiviral vaccine or therapy is not available to work against EBOV infection in humans. However, supportive recovery practices are performed include high-fluid intake (10L per day in the first 72 h), ventilator support and broad-spectrum antibiotic therapy. The present review describes briefly about virology, epidemiology, pathophysiology, transmission, clinical manifestation, diagnosis and treatment of ebola viral disease.

Keywords: *Ebola virus disease, Ebola hemorrhagic fever, Ebola virus, Africa, Filoviridae, Immunoevasion.*

Introduction

The Ebola virus is classified under the family filoviridae, the genus ebolavirus, has a lipid-envelop with negative stranded RNA and also one of the most harmful human pathogen (WHO, 2015; Feldman H *et al.*, 2013). The transmittance of Ebola virus by broken skin or mucous membrane, urine, feces, vomit, saliva and contaminated needles (Feldman H *et al.*, 2011; Colebunders R *et al.*, 2000). Ebola hemorrhagic fever (EHF) is an acute viral fever shows multiple nonspecific-disease symptoms include high fever, vomiting, headache, anorexia, aching muscles and diarrhea. In advance stage, EHF causes bleeding from the nose, eyes and gastrointestinal region (Feldman H *et al.*, 2011; Sureau PH, 1989; Baize S *et al.*, 2014). EHF epidemic is caused by five different species of the genus, ebolavirus: *Zaire ebolavirus, Sudan ebolavirus, Bundibugyoebolavirus, Côte D'Ivoireebolavirus* and *Reston ebolavirus*. One human case has been reported with EHF is caused by *Côte D'Ivoire ebolavirus* (Le Guenno B *et al.*, 1995). *Reston ebolavirus can cause disease only in non-human primates (NHP) especially was found in swine* (Barrette RW *et al.*, 2009). *The most of EHF epidemic is caused by* Zaire, Sudan and Bundibugyo Ebola viruses. In which, Zaireebolavirus can be a serious threat to human and NHPs in west Africa. EHF associated with zaire established high mortality rate of 90% than the rest of other strings of ebolaviruses (Feldmann H *et al.*, 2004; Groseth A *et al.*, 2007; Towner JS *et al.*, 2008). The first outbreak of Ebola virus disease (EVD) was reported in the Democratic

Republic of Congo in 1976. Since then, several reports of small outbreaks were appeared in countriesin central Africa that include Sudan and Uganda (Burke J *et al.*, 1978; Muyembe-Tamfum JJ *et al.*, 2012). In these countries, 2000 plus cases were occurring in between the years 1970 to 2013. The first outbreak was seen in Guinea, the country of West Africa, and it was spreadrapidly and created a serious epidemic inneighboring countries like Liberia and Sierra Leone (Chowell G *et al.*, 2014). The west Africa Ebola outbreak 2014 was believed to be most terrified incidents in medical history in regard of the number of human cases and mortalities (Bausch DG *et al.*, 2014; Enserink M, 2014; Green A, 2014; Ansumana R *et al.*, 2014). In recent times, the rural and urban areas of Nigeria were affected severely by Ebola outbreak. Several experienced non-governmental and governmental organizations have been working actively in the field to control the epidemic (Baize S *et al.*, 2014), but failed due to many factors include disease denial in the context of strong religious beliefs, population, poverty, authorities' distrust, inadequate salaries and lack of adequate protection for health care workers and weaknesses in public health systems.The World Health Organization (WHO) has declared a public health emergency of international concern and also called all nations for a coordinated international response to investigate, detect and manage Ebola cases (Hawkes N, 2014). The current review is briefly describing all the necessary information regarding Ebola virus disease.

Ebola Virus Disease Outside Africa

EVD has also been spread to outside Africa include America and Europe. The risk of EVD was minimum in high-income countries due to the implementation of adequate infection control procedures. Physicians must have the abilities to handle and manage the EVD patients in emergency or intensive care units (ICU). Providing appropriate treatment and prevention of human-to-human transmission of Ebola virus are the main objectives of any physician for the effective control of spreading EVD.

Ebola Epidemic In The West Africa

Airborne transmission of Ebola virus between humans has not been reported. In the early stage of EVD, symptoms are similar to those of typhoid, malaria and Lassa fever.Thus, early symptomatic diagnosis of EVD is very difficult in comparison of other virulent diseases.

Virology of Ebov

Virions have different morphological forms of long filamentous rods or convoluted shapes. Virions of the EBOV genome are made with a core of single negative-sensed RNA, also contain proteins such as viral proteins 24, 30, 35 and 40, nucleoprotein, L protein and glycoprotein (GP). The structural similarity of genome among the species brings a wide genetic divergence. In addition, phylogenetic analysis of GP gene sequences of EBOV confirmed that epidemic EBOV-Z strains shown close genetic relationships (Mehedi M *et al.*, 2011; Maganga GD *et al.*, 2014).

Epidemiology

The filovirushemorrhagic fever was primarily recognized in Germany and Yugoslavia in 1967. The causative virus was named as Marburg virus (Siegert R *et al.*, 1967) Southern Sudan and Northern Zaire were affected with an epidemic of hemorrhagic fever was reported in 1976. In the name of Ebola River, located in the north western Democratic Republic of the Congo, an uncertain infectious agent was named as theEbola virus. In 1994, the third Ebola virus species were found in the Tai forest where an ethnologist had performed the post-mortem examination on chimpanzee was living with other members of its species were dying due to EHF (Le Guenno B *et al.*, 1995). Other Ebola virus species also had existed that include Bundibugyoebola virus from the equatorial region of Africa (Towner JS *et al.*, 2008) and Reston Ebola virus, non pathogenic for humans discovered (1989) in Reston, Virginia, USA (CDC, 2009). The Ebola virus had primarily identified in the area of the rain forests of Central Africa. In recent, it entered epidemically to the distant villages of Central and Western Africa. WHO, CDC (Center for Disease Control), and many international associations have updated the recent knowledge about EVD to students, travelers and clinicians.The high fatality rate (60-90 %) of EVD outbreaks depends on the accessibility of appropriate medication, time of diagnosis, and EVD subtype (WHO, 2014).

Pathophysiology

The Ebola virus is an intracellular parasite contains a filamentous structure enveloped with non-segmented RNA (single strand). Five distinct genomes of Ebola virus (ZEBOV,BDBV,REBOV,TAFV and SEBOV) differ in location of gene overlaps and gene sequence. Amongst these, VP35, VP30, nucleoprotein and RNA-dependent RNA

polymerase are responsible for viral replication and transactivation. VP24 is the matrix protein and associated with nucleocapsid formation. In addition, VP40 is accompanied by budding and delivery of viral particles. Both the VP24 and VP40 are responsible for obstructing interferon signalling. EVD shows six phases of viral replication: attachment, penetration, un coating, replication and expression , maturation and delivery/release of the virus.

Pathogenesis And Transmission

The transmission of Ebola virus is due to close reside with the wild animals like chimpanzees, baboons, African green monkeys, duikers and fruit bats (*Myonycteristorquata*and*Pteropodidae, Hypsignathusmonstrosus*, *Epomopsfranqueti* (Groseth A *et al.*, 2007). Plants, birds and arthropods were become as possible reservoirs of ebola virus (CDC, 2015). EVD outbreaks (2001 & 2003) with traces of ZEBOV were found in the carcasses of chimpanzees and gorillas are the source of human infections. The first Ebola outbreak in Congo was due to reusage of unsterilized needles and syringes were a crucial factor in the transmission of Ebola virus. The Kikwit outbreak of Ebola virus was because of improper protective measures of several clinicians (Khan AS *et al*., 1999; Muyembe-Tamfum JJ *et al.*, 1999). The multiplication of Ebola virus is occurring in macrophages, monocytes and dendritic cells through which virus elements distribute to spleen, lymph nodes, liver and other organs of the body.The persistence capability of Ebola virus is higher in the dried state and also within body fluids (Olejnik J *et al.*, 2011; Geisbert TW *et al*., 2003). The fatality of EHF was due to the evidence of the increase of interferon-alpha and gamma, interleukin - 2 and 10 and tumour necrosis factor in blood.More noticeable effects caused by Ebola virus include changes in vascular permeabililty, microvascular damage and activation of the clotting cascade and also involve in impairment of endothelial cells and platelets cause imbalance of homeostasis.The persistence of virus in semen up to 7 weeks it indicates that the probability of ebola transmission in sexual mode.The spread of EBOV infection to infants through breast milk, making the kid infected (Feldmann H *et al.*, 2011).

Ebola Immune Evasion Mechanisms

Ebola virus antagonizes the IFN-a and IFN-b responses in monocytes, macrophages and DCs, preventing host inborn immunity for functioning normality. In addition, EBOV infection in a human liver cell (Huh7) antagonizing the key antiviral responses that include TLR and protein kinase related pathways, but RESTV infection of Huh7 cells shows a siginificant increase of IFN-stimulated genes (Kash JC *et al.*, 2006). So it concludes that an indirect correlation existed between virulence in humans and the magnitude of IFN-a/b responses (Kash JC *et al.*, 2006).

Transmission Routes

EBOV infected bats and simians areone of the primary sources of EBOV when these are consumed or handled by humans (Groseth A *et al.*, 2007).Extreme care must be taken to handle the body fluids of EVD patients to avoid infection (Chowell G *et al.*, 2014). Because all human-to-human EBOV infections are because of direct contact with body fluids and/or blood (e.g. Mucus, saliva, vomit, sweat, feces, tears, semen and urine) of symptomatic or dead patients (Chowell G *et al.*, 2014).

Clinical Manifestations

ZEBOV has the most severe mortality rate of 90%, where asSudan ZEBOV (SEBOV) have shown 53-66% mortality rate (Baron RC *et al.*, 1983; Towner JS *et al.*, 2004). An incubation period of EVD is 2-21 days (Avg. 4-10 days). Severely infected patients die within 6-9 weeks after the first symptoms appear. In most outbreaks, slow disease identification leads to increasing the death rates due to unfamiliar and non-specific symptoms of new illness are difficult for physicians to identify at initial stage.

Clinical Features of Evd

EVD develops respiratory symptoms (chest pain and cough), systemic gastrointestinal (vomiting and diarrhea),neurological (confusion, headache andcoma) symptoms and vascular edema (Feldman H *et al.*, 2013; Feldman H *et al.*, 2011; Muyembe-Tamfum JJ *et al.*, 2012). Hemorrhagic symptoms may cause ecchymosis, petechiae and uncontrolled mucosal hemorrhage (Feldman H *et al.*, 2013; Feldman H *et al.*, 2011; Muyembe-Tamfum JJ *et al.*, 2012). These complications cause multiple organ failure that may lead to death. The nonspecific laboratory data of EVD

are also a factor for the higher mortality rate with Ebola virus (Feldman H *et al.*, 2013; Feldman H *et al.*, 2011; Jeffs B, 2006). In the early stage, an evident of lymphocytopenia and leukocytopeniain peripheral blood, and also thrombocytopenia and neutrophilia are mostly seen in blood (Feldman H *et al.*, 2013; Feldman H *et al.*, 2011). In nonfatal condition, a high fever continues up to 5-9 days, but improved symptoms seen during 7-10 days after onset (Feldman H *et al.*, 2013; Feldman H *et al.*, 2011; Ksiazek TG *et al.*, 1999). In the early stage of EVD, no specific symptoms found to diagnose the disease. Hence, laboratory test includes humoral antibody response is essential to confirm the EVD (Feldman H *et al.*, 2013). Immunological methods (ELISA) and/or RT-PCR have generally used techniques for detection of other viral infections (Feldman H *et al.*, 2013).

Diagnosis

The diagnosis of EVD is quite difficult as it needs a complete history as well as a full examination of disease and its causative agent. In endemic countries, Ebola virus infection is due to eating or hunting of animals or bats, close contact with dead bodies or ill persons. The diagnosis of the Ebola virus in disease prevalent countries or outbreak affected areas can be performed using ELISA, PCR, immune fluorescent and histochemistry methods. The Ebola virus is largely found in dermal tissues. Thus, skin biopsies are performed for post-mortem confirmation of Ebola viral infection. In earlier, serological tests were carried out using the indirect fluorescent antibody method for the detection of Ebola virus infection. But these tests had difficulties of sensitivity and unambiguity renders the test as ineffective. Thus, a direct IgG ELISA assay method substituted the indirect fluorescent antibody method for prevalence evaluations (Guimard Y *et al.*, 1999; Ksiazek TG *et al.*, 1999; Zaki SR *et al.*, 1999; van der Groen G *et al.*, 1978; Tomori O *et al.*, 1999; Busico KM *et al.*, 1999). In 1995, Dr.SherifZaki diagnosed an Ebola virus in formalin-preserved skin biopsies using a colorimetric assay method. Few additional tests include complete blood count, liver enzymes, metabolic panels and coagulation studies are also important for the diagnosis of EHF (CDC, 2014; Gatherer D, 2014; McElroy AK *et al.*, 2014). Other serological tests such as indirect immune fluorescence test also can be employed for examination of Ebola virus. Sophisticated diagnostic tests include a micro-array based assay and multiplex PCR are developed on the symptoms of the common clinical disorder (Sanchez A *et al.*, 2007).

Treatment

There is no specific remedy for EHF. The treatment is mainly on the basis of supplying proper hydration, control of organ failure and nutritional support with antibiotics. There were no specific vaccine and no successful antiviral drug was available for preventing Ebola virus infection. The safety procedures as per CDC guidelines such as personal protective instruments, surface cleaning, etc. should be employed to protect from the risk of infection caused by dead bodies (CDC, 1998). In the 1995, clinical investigation was performed on the Ebola epidemic in Kikwit, eight Ebola patients were subjected to passive immunization (blood transfusion) and seven of them were improved in their health condition and stayed alive (Mupapa K *et al.*, *1999*). Such types of studies were not considerable in further Ebola outbreaks. An in vitro assay indicates that Ebola had no neutralizing action against antibodies. In addition, monoclonal antibodies exhibited healing and defensive properties against Ebola virus in mice, but these antibodies were unable to protect nonhuman primates (Gupta M *et al.*, 2001*;* Oswald WB *et al.*, 2007). The uses of various routes of administrations include catheters, injections and parenteral interventions, etc. were minimized to control trauma and spreading of disease. Drugs like aspirin, NSAIDs, anticoagulants and steroids are strictly contraindicated (Borio L *et al.*, *2002*). For several years, extensive research work has been conducted to find the appropriate drug for effective cure of patients with EVD.

Currently, several classes of drugs are available to act against Ebola infection include monoclonal antibodies (ZMapp),RNA inhibitor based (TKM-Ebola) agents, antisense-based(AVI-7537) drugs and positively charged phosphorrodiamidatemorpholino oligomers. Favipiravir (T-705) is a pyrazinecarboxamide derivative, acts as a viral replication inhibitor. ZMapp is one of the most recommended drug, mainly targets the expression phase of viral replication. It consist of three monoclonal antibodies, inhibits the replication of virus by binding to the protein of the EBOV (WHO, 2014). Another potential drug, BCX4430 shows antiviral activity for Ebola, Marburg and yellow fever, has capability to target an enzyme present in these specific viruses. It is also effective for small animals if they are treated after infection within 48 h (Editorial, 2014). The off-label use of angiotensin-converting enzyme inhibitors, statins and angiotensin receptor blockers and are also advised because of their ability to induce

immunity to the infected person.The Ebola virus is generally considered to be conceivable biological weapon; hence there is an essentiality to discover effective antiviral vaccines and drugs.

Vaccines And Treatment: Ethical Issues

In sub-Saharan Africa, more than 15 Ebola outbreaks have exploded since 1976, therapeutic drug remain undeveloped yet. No licensed vaccines or immune-mediated treatments or specific antiviral drugs are available for post exposure prophylaxis patients. The US National Institute of Health supports clinical trial team to conduct phase 1 studies on new prototype of experimental vaccine.The WHO expert committee implemented an assessment of bioethical implications for providing advanced access to experimental prophylaxis of EVD. Ethical considerations required, especially for health workers who work in high risk areas. These moral principles should give priority and benefit to patients as well as target the control of spreading of disease in the community or hospitals. National leaders must take the initial steps to increase the productivity and availability of scarce vaccine and medications to the patients of EVD.

Present Status of Therapeutic Drug Developments For Evd

Currently, no approved definitive medication such as anti-viral drugs or vaccines is available for treating EVD (Feldmann H *et al.,* 2011; Muyembe-Tamfum JJ *et al.,* 2011). Thus, suggestive treatment methods include antibiotics and/or electrolytes are normally used (Feldman H *et al.,* 2013*;* Feldmann H *et al.,* 2011). Two promising vaccines have been reported against EVD till date. GlaxoSmithKline and The US National Institute of Allergy and Infectious Diseases have developed one promising EVD vaccine (i.e. cAd3-ZEBOV) is a chimpanzee derived vaccine consists adenovirus vector in which Ebola virus gene was previously inserted (Kanapathipillai R *et al.,* 2014). The Public Health Agency of Canada in Winnipeg has developed the second vaccine known as rVSV-ZEBOV (Jones SM *et al.,* 2005). The clinical availability of these vaccines is expectedly to be beginning soon. ZMapp contains 3 monoclonal antibodies; the drug is designed to prevent the EBOV infection in monkeys by neutralizing the GP protein of Ebola virus (Qiu X *et al.,* 2014). Two American EVD patients previously infected with EBOV were recovered from EVD by taking a proper dosage regimen of ZMapp, but unfortunately a Spanish patient was died with the same drug (WHO, 2014). The effectiveness of this experimental medication was not known yet. Favipiravir, a nucleic acid analog antiviral drug is the most appropriate drug under drug development category for the treatment of EVD (Gatherer D, 2014). Earlier, this drug was used to treat influenza (Gatherer D, 2014; Furuta Y *et al., 2013*) by inhibiting the RNA dependent RNA polymerase (RdRp) of influenza virus is responsible for the synthesis of viral RNA (Furuta Y *et al., 2013*). The similarity in the mechanisms for the synthesis of viral RNA between influenza and Ebola viruses is expected to be provided a similar drug effects on RNA synthesis of Ebola virus (Smither SJ *et al., 2014*). Thus, favipiravir has been trying clinically as a potential drug for prevention of EVD epidemic.

Public Health Counter Measures

The classic public health measures should be taken as standard responses to control and/or prevent the EVD.

Isolation and Quarantine: EVD affected states must invoke multiple forms of quarantine, educate patients about EBOV epidemic and guide them to stay-at-home as home confinement. The military should deploy house-to-house searches, traveler checkpoints and separating people who belong to other countries. The incubation period of EVD lasts up to 3 weeks and careful monitoring and enforcement is required for delivery of compulsory services like food, medication, etc.

Social Distancing: Governments should invoke people to maintain social distancing in epidemic regions. Public gathering includes sports, entertainment and shopping must be avoided.

Risk Communication and Burial: Governments have the responsibility to educate public by providing accurate risk communication without delaying news coverage on EBOV infection (Williams WCL, 2014). The cremation of bodies has to perform according to the guidelines given by the Ministry of health. There is a need to prevent traditional burial processes being continued in several areas yet.

Travel Restrictions: The spread of Ebola by airline travel made border regions of West Africa in danger. Nigeria is a real victim of EBOV epidemic through improper implementation of air traffic restrictions. The Nigerian Government has taken precautionary measures to control the most serious threats by temporarilysuspending of

flights or screening of all foreign passengers, etc. The US CDC issued 3rd level travel warning indicates a serious threat for the Nigerian people.

Health Care Settings: Healthcare facilities such as isolation units, trained staff, strict infection control, personal protective equipment and hospitals are controlling points for spreading of EBOV infection. Improper clinical facilities made 140 African health workers infected, in which 80 workers were died (Hinshaw D *et al., 2014*).Inadequate salaries and the shortage of human resource in the epidemic region are the key factors placing health care professionals at high risk. Ethical dilemmas of health workers also playing a role in EVD epidemic that include reporting duty without sufficient personal protective equipment, unhygienic cleaning procedures while handling body fluids or blood.

Guidelines for treating EVD patients are immediately required. Hence, WHO should take an initial step towards the leadership and development of guidelines to treat EVD. These guidelines must give the information regarding diagnosis of Ebola virus disease, principles of measurement and correction of electrolyte imbalance, intravenous fluid replacement, HIV testing and implementation of EVD testing facilities.

Conclusion

Ebola virus infection has been a serious threat to human individuals due to its highly infectious and lethal behaviour since it was discovered in 1976. Ebola hemorrhagic fever is one of the most identified fatal fever with no specific medication is available. The spreading of disease mainly through the transmission of blood and body fluids from one person to another person due to inadequate hygienic procedures. There is an immediate requirement of conveying the information to the public and conducting training programmes for health care professionals and other hospital staff.The best method to minimize the Ebola epidemic cases is to control the spread of the disease. And more healthcare programmes are required to conductin a large scale for developing the awareness about Ebola virus disease, its preventive measures and eradication process.Extensive research investigations are needed to develop an accurate diagnostic procedure as well as an affordable and easily available medication for the treatment of Ebola virus infection.

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