

A REVIEW ON EBOLA VIRUS: SPECIFYING EPIDEMIOLOGY, PATHOGENESIS AND ITS TREATMENT APPROACHS

Gajendra Vasu*, Nidhi Jain M.Pharm, Sapna Malviya Ph.D. and Anil Kharia

Modern Institute of Pharmaceutical Sciences, Indore, M.P.

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*Corresponding Author

Gajendra Vasu

Modern Institute of
Pharmaceutical Sciences,
Indore, M.P.

ABSTRACT

Ebola virus disease is one of the most deadly ailments known to mankind due to its high mortality rate (up to 90%). Ebola hemorrhagic fever is an infectious disease of animal that can be transmitted to both human and non-human primates. The first epidemic of Ebola hemorrhagic fever occurred in 1976 in the Democratic Republic of the Congo. The incubation period of Ebola is less than 21 days. Ebola virus infections are depicted by immune suppression and a systemic inflammatory response that leads to damage of the vascular, coagulation and immune systems, causing multi-organ failure and

shock. Five genetically distinct members of the *Filoviridae* family responsible for Ebola hemorrhagic fever are as follows: *Zaireebolavirus*, *Sudan ebolavirus*, *Tai Forest ebolavirus*, *Bundibugyo ebolavirus* and *Restonebolavirus*. The ongoing 2014 West Africa Ebola epidemic has been considered as the most serious panic in the medical field with respect to both the number of human cases and death toll. The natural host for Ebola virus is unknown, but on the basis of evidence and the nature of similar viruses, researchers believe that the virus is animal-borne and that bats are the most likely reservoir. The Ebola virus infection provides little chance to develop acquired immunity causing rapid progression of the disease. It is pertinent to mention that at present, there is no antiviral therapy or vaccine that is helpful against Ebola virus infection in humans.

KEYWORDS: Ebola Hemorrhagic Fever, Vaccines, Outbreak, Marburg Virus, Filoviridae.

INTRODUCTION

The Ebola virus disease is a fatal disease that is being continuously reported in the past decade.^[1] Ebola virus diseases (EVDs) have always been a challenge and a global menace since its discovery in 1976 by Dr. Peter Piotin in Zaire, Africa (now Democratic Republic of

Congo) from the blood of a catholic nun who suspected of having yellow fever.^[2] Ebola hemorrhagic fever (EHF) is a zoonotic disease transmitted accidentally by direct contact with infected live or dead animals. EHF is an acute viral syndrome with fever and subsequent bleeding diathesis marked by high mortality in human and nonhuman primates (monkeys, gorillas and chimpanzees). EVD is characterized with symptoms and signs of fever, focal necrosis of the liver, kidney and spleen bleeding diathesis, fulminate shock resulting in death with a mortality rate reaching 90%.^[3,4] Nonetheless, during the early diagnosis of the EBOV, hemorrhagic manifestations were the most prominent features seen in patients who died.^[5] The Filoviridae consist of three general names known as EBOV, Marburg virus (MARV) and Cuevavirus.^[6] EVD is also considered to be a category A agent and potential bioweapon agent.^[7] The first outbreak of an unknown infectious disease (Marburg disease) was reported in Germany and Yugoslavia in the year 1967. An estimated 31 persons were affected in which 7 persons died. Eventually, a new strand of the virus was extracted from a patient and was traced back to velvet monkey imported from Uganda. The disease was named the 'Marburg disease' because it was located in the West German town of Marburg.^[8]

Epidemiology: The EBOV has a case fatality rate of 30% to 90% and increased frequency in the African region due to weaker health infrastructure and services. Looking at the 2014 EBOV disease (EVD) outbreak in West Africa, as of September 14, 2014, a total of 4507 probable and confirmed cases, including 2296 deaths from EVD (Zaire species) had been reported from five countries in West Africa Guinea, Liberia, Nigeria, Senegal and Sierra Leone. The World Health Organization Ebola Response Team analyzed a detailed subset of data on 3343 confirmed and 667 probable Ebola cases collected from the five countries and found out that the majority of the patients are 15-44 years of age with 49% male.^[9]

Virology: The EVD, previously known as EHF is a severe condition caused by a virus belonging to genus *Ebola virus*, family *Filoviridae* and order *Mononegavirales*.

The EBOV is sub-divided into five species.^[9]

1. Zaire Ebola virus (ZEBOV).
2. Sudan Ebola virus (SEBOV).
3. Tai forest Ebola virus (TAFV).
4. Bundibugyo Ebola virus (BDBV).
5. Reston Ebola virus (REBOV).

BDBV, ZEBOV and SEBOV have been accompanied with large EVD epidemic near the tropical rainforests of Central and West African distant villages; among these three ZEBOV are responsible for high mortality rates in humans. REBOV and TAFV were not accustomed for illness or mortality inhuman.^[10,11]

Pathogenesis and Transmission: The wild animals like primates (chimpanzees, gorillas, baboons, duikers and African green monkeys) and fruit bats (*Hypsignathusmonstrosus*, *Epomops franqueti*, *Myonycteris torquata* and *Pteropodidae*) are the natural hosts for the EVD and are responsible for transmission of Ebola virus from animals to humans.^[12]

In humans the disease can be transmitted by the following methods

1. Coming into contact with the blood, secretions, organs or other bodily fluids of an infected person.
2. Contact with the bodily fluids of an infected person who has passed away.
3. Handling the meat from infected animals.
4. Exposure to objects (such as needles) that have been contaminated with infected secretions.
5. Healthcare workers may contract the disease through transmission as well through contact with infected bodily fluids.^[13]

Diagnosis: The approach to evaluate patients with possible Ebola virus disease depends upon whether or not the individual displays appropriate signs and symptoms.

Key symptoms that should be a definite of the presence of the Ebola virus include the following

1. Acute febrile illness
2. Headache, myalgia, nausea, vomiting, diarrhea and abdominal pain
3. Bleeding with unknown reason
4. Sudden death with unknown reason.^[14]

Epidemiologic conditions, with any of the following 21 days before onset of symptoms

1. History of travel from or living in the endemic area of EVD.
2. Exposure of blood, body fluids or discharge pollutants from possible or defined cases.
3. History of contact with bats, rodents, or primates in endemic area of EVD.
4. Operate the specimen of EVD in a laboratory.^[14]

Ebola virus infections can be diagnosed in the laboratory by a number of different tests

1. ELISA
2. Antigen detection tests
3. Serum neutralization test
4. RT-PCR assay
5. Virus isolation by cell culture.^[15,16]

Clinical Features

The onset of the disease is abrupt after an incubation period of 2 to 21 days. The clinical features can be divided into four main phases as follows

Phase 1- Influenza-like syndrome: The onset is abrupt with nonspecific symptoms or signs such as high fever, headache, arthralgia, nausea, sore throat, and myalgia.

Phase 2- Acute (days 1-6): Persistent fever not responding to ant malarial drugs or to antibiotics, headache and intense fatigue followed by diarrhea and abdominal pain and vomiting.

Phase 3- Pseudo-remission (days 7-8): During this phase the patient feels better and seeks food. The health situation presents with some improvement. Some patients may recover during this phase and survive from the disease.

Phase 4- Aggravation (day 9): In many if not most cases, the health status gets worse. The following symptoms may be observed:

- Skin manifestations: petechiae (not so obvious on black skin), purpura (morbilliform skin rash)
- Respiratory disorders: dyspnea, cough, hiccups, throat and chest pain,
- Cardiovascular distress and hypovolemic shock.

Based on these clinical manifestations, it is obvious that at the start of EHF, the disease can mimics many other tropical diseases such as malaria or typhoid fever. In most outbreaks, recognition of EHF is delayed because physicians are not accustomed to seeing this illness and its symptoms are generally nonspecific.^[17]

Prevention: The best way to prevent the EVD is by not traveling to areas where the virus is found. If you are in areas where Ebola is present, avoid contact with bats, monkeys,

chimpanzees, and gorillas since these animals spread Ebola to people. Health care workers can prevent infection by wearing masks, gloves, and goggles whenever they come into contact with people who may have Ebola.^[18] People should not have contact (or eat) with blood, meat or body fluids of animals which show signs of Ebola virus disease. For at least several months after recovery and until advised otherwise by a doctor, males who have had Ebola virus disease should use a condom when engaging in sexual intercourse. Individuals with suspected or confirmed Ebola virus disease need to be isolated and excluded from childcare, preschool, school and work until cleared to return by a doctor.^[19]

Treatment

There is no specific treatment or vaccine for Ebola. Severely ill patients must be given symptomatic treatment and intensive care. The therapeutic approach is based on

- Palliative care: rehydration is essential (oral or others depending on circumstances), maintenance of electrolyte balance (for example, with a potassium supplement), kidney and liver function support.
- Symptomatic treatment: painkillers, anti-emetic against vomiting, anxiolytics to combat anxiety, antibiotics, antimalarial remedies.
- Intensive care: use of oxygen in the event of severe bleeding and if intravenous therapy is an option transfusion of blood or previously tested blood components (red blood cells, platelet concentrates, fresh frozen plasma)
- Use of equipment to monitor biochemical and blood values of patients to maintain the electrolyte balance.
- The use of products containing salicylates (i.e., acetylsalicylic acid/aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDS) is prohibited.
- At the current state of knowledge, serotherapy is not recommended for the treatment of Ebola or Marburg.
- Outcome of the laboratory diagnostic test for Ebola (important for classifying suspected cases in the field, for prognosis when the presence of antibodies is detected, and for discharge of patients).

Several candidate vaccines are being developed, but it will be another few years until outbreak response teams working in the field will have vaccines available.^[25]

1. Recombinant nematode anticoagulant protein c2 (rNAPc2)

When the organs are affected, this results in coagulation inhibitor depletion which in turn causes dissemination intravascular coagulation. In the dissemination intravascular coagulation, the tissue factor (a substance present on a cell but not in contact with blood) combines with factor VII for clotting formation^[20]. However, the rNAPc2 inhibits factor VII and the tissue factor whereby providing partial post exposure protection to rhesus. rNAPc2 can be useful in the fight against other viral hemorrhagic fevers because it targets the disease process. It can be referred to as having a suitable pharmacokinetic and safety profile in humans.^[20,21]

2. Recombinant human activated protein C (rhAPC)

The activated protein C is generated from protein C, it was recognized that infected NHPs have decreased level of protein C when infected with EBOV. This is because the infection targets protein C which is produced in the liver. Therefore, experiments were conducted to demonstrate the efficiency of rhAPC in protecting NHPs from the EBOV. The outcome concluded that 2 out of 11 were protected from the lethal EBOV challenge. This product was created as a single dose post exposure treatment but since the treatment does not target the virus, there may be merit in analyzing the treatment in conjunction with a direct antiviral.^[17]

3. RNA interference (RNAi)

RNAi represents a powerful process which inhibits gene expression with a regulated enzyme-mediated process. The small interfering RNA targeted the polymerase L protein of the Zaire Ebola, which formulated a stable nucleic acid-lipid particle. This phenomenon protected the guinea pig shortly after infected with the EBOV. This treatment was then tested in rhesus macaques, which 35 formulated instable nucleic acid-lipid particles. Eventually, three of the monkeys were given four doses and as a result two survived the infection. However, eleven monkeys were given seven doses and all survived the infection.^[22]

4. Phosphorodiamidate morpholino oligomers (PMOs)

At the point in time, most researchers focused on therapeutic strategies that bolstered the host immune response or inhibit in viral replication. As a result, two researchers decided to use a different approach a substance called PMO. PMO exerts a hindrance of gene translation by blocking ribosomal assembly. As such, the EBOV specific is combined with the PMO which targets the viral mRNA in acquiring the VP24 and VP35. This has resulted in the protection of mice in pre-exposure and post exposure from the lethal Ebola challenge. Afterwards, AVI-

6002 was developed which is known as the combination of PMOs against EBOV VP24 and VP35 which is currently in phase I clinical trials. These PMOs, provided 30-60 min of post exposure, approximately more than 60% of rhesus macaques were protected from the Ebola infection. The PMO has been tested in humans and it was considered to be safe and can be produce in large amounts.^[23]

5. MB-003 monoclonal antibody cocktail

Recently, antibodies have proven to be efficacious for post exposure treatment against the EBOV in NHPs. Protection was seen in rhesus macaques when passive transfer of macaque hyperimmune globulin was inoculated 2 days post-exposure. Another case concluded that a cocktail of three murine monoclonal antibodies successfully provided 100% protection in cynomolgus macaques administered within the first day but 48 h after, the cocktail provided 50% protection against the lethal EBOV challenge. Lastly, a mixture of three monoclonal antibodies (MB-003) produced in a plant called the *Nicotianabenthamiana*. This product provided 100% or 65% protection from the lethal Ebola challenge with no clinical manifestation, when administered 1 or 2 day's post-exposure respectively.^[24]

CONCLUSION

Current study shows that Ebola virus has been a threat to human health due to its dangerous, highly lethal and infectious behavior. Ebola fever has come out as one of the most fatal identified forms of hemorrhagic fever, for which there is no specific remedy available. The spread among humans occurs mainly through the exchange of blood and body secretions. Other noticeable forms of transmission include hospital acquired infection and inadequate hygiene practices. There should be urgent requirement of spreading of information to community and training programs for doctors, nurses and other hospital staff.

The future endeavors require the emphasis on the understanding of the differences among species of Ebola virus. The research should also essentially be focused on establishment of rapid and simple diagnostic kits for Ebola infection. It is anticipated that outcome of research investigations would result in development of easily available and affordable drug for the treatment of Ebola virus. Tremendous amount of experiments have been conducted to develop drugs and vaccines which can prevent the spread of this dreadful virus. Animal models such as mice, guinea pigs, hamsters and NHPs have been used to test the effectiveness or safety of the vaccines or drugs developed.

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