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## EBOLA VIRUS -A Review

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### ABSTRACT

This review focuses on Ebola, a deadly virus of the family Filoviridae that damages the immune system. Since the initial discovery of *Zaire* and *Sudan ebola virus* in 1976, the Ebola viruses have been responsible for severe hemorrhagic fever outbreaks in Africa with case fatality rates between 40-90% and Zaire strain showing maximum fatality rate. Most people are infected by giving care to infected people either directly or by cleaning the infected person's body fluids. Further the review also addresses the signs and symptoms of the disease which is characterized by symptoms like fever, muscle pain, headache, nausea, diarrhea, rash and so on during the early stages of the disease. This disease could be diagnosed through laboratory findings by several detection tests like IgM Elisa, Immunosorbent Assay technique, Polymerase chain reaction (PCR), Immunohistochemistry testing, isolation of viruses and so on. New drug therapies are evaluated but no FDA approved drug is available, only some supportive care like providing fluids, replacing blood, treating some infections developed is provided to patients suffering from Ebola. Currently ZMapp is being tried which is a combination of three monoclonal antibodies.

**Key Words:** Ebola, Virus, Zaire, Hemorrhage, Endothelium, Antibodies.



### INTRODUCTION

Ebola haemorrhagic fever (EHF) is caused by the Ebola virus, a member of the Filoviridae family [1]. Ebola, previously known as Ebola hemorrhagic fever, is a rare and deadly disease caused by infection with one of the Ebola virus strains. Ebola can cause disease in humans and nonhuman primates (*monkeys, gorillas, and chimpanzees*). Ebola is caused by infection with a virus of the family Filoviridae, genus *Ebolavirus*. There are five identified Ebola virus species, four of which are known to cause disease in humans: Ebola virus (*Zaire ebolavirus*); Sudan virus (*Sudan ebolavirus*); Tai Forest virus (*Tai Forest ebolavirus*, formerly *Cote d'Ivoire ebolavirus*); and Bundibugyo virus (*Bundibugyo ebolavirus*) [2]. The fifth, Reston virus (*Reston ebolavirus*), has caused disease in nonhuman primates, but not in humans. Reston virus was shown by researchers at the Centers for disease Control and Prevention (CDC) to be antigenically and genetically distinct from the African Ebola viruses, yet despite its high pathogenicity for nonhuman primates, it did not appear to cause disease in humans. Several persons

who handled the infected animals developed antibody to Ebola virus but showed no signs of disease; one of these persons was infected while performing an autopsy on an animal died of a Reston virus infection. In 1992, a repeat of the 1989 Reston episode occurred in Siena, Italy when macaques were received from the same Philippine exporter; no evidence of a human infection was found [3].

### STRUCTURE AND CLASSIFICATION OF THE EBOLA VIRUS

Ebola virus and the related Marburg virus are members of the Filovirus family, which are pleomorphic, negative-sense RNA viruses whose genome organization is similar to the Paramyxoviridae. Of the four identified strains of Ebola virus, three—the Zaire, Ivory Coast, and Sudan strains have been shown to cause disease in both humans and nonhuman primates, with the Zaire strain exhibiting the highest lethality rate [4,5]. The only documented outbreaks of Ebola virus infection in the United States were restricted to nonhuman primates at holding facilities in

Virginia and Texas, caused by the Reston strain, which has not yet caused fatal disease in humans [6]. The Ebola virus genome is 19 kb long, with seven open reading frames encoding structural proteins, including the virion envelope glycoprotein (GP), nucleoprotein (NP), and matrix proteins VP24 and VP40; nonstructural proteins, including VP30 and VP35; and the viral polymerase [7]. Unlike that of Marburg virus, the GP open reading frame of Ebola virus gives rise to two gene products, a soluble 60 to 70 kDa protein (sGP) and a full-length 150 to 170 kDa protein (GP) that inserts into the viral membrane [8,9] through transcriptional editing (Figure 1 and 2).

## HISTORY OF EBOLA

In 1976, Ebola (named after the Ebola River in Zaire) first emerged in Sudan and Zaire [10]. The first outbreak of Ebola (Ebola-Sudan) (SEBOV) infected over 284 people with a mortality rate of 53%. A few months later, the second Ebola virus emerged from Yambuku, Zaire, Ebola-Zaire (ZEBOV). ZEBOV, with the highest mortality rate of any of the Ebola viruses (88%), infected 318 people. Despite the tremendous effort of experienced and dedicated researchers, Ebola's natural reservoir was never identified. The third strain of Ebola, Ebola Reston (EBOR), was first identified in 1989 when infected monkeys were imported into Reston, Virginia, from Mindanao in the Philippines. Fortunately, the few people who were infected with EBOR (seroconverted) never developed Ebola hemorrhagic fever (EHF). 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, Cote d'Ivoire, accidentally infected herself during the necropsy.

A large outbreak then occurred in 1995, around the town of Kikwit, south of (Democratic Republic of Congo) DRC, with 315 cases and a mortality rate of 81% [11]. The third outbreak occurred in 1996–1997 with 60 cases and 45 deaths over a 6-month period. Fifteen cases and 11 deaths were recorded in Libreville, the capital of Gabon, and a South African nurse was infected by a Gabonese physician who had travelled to Johannesburg. The period 2000–2008 was marked by repeated ZEBOV outbreaks, SEBOV resurgence, and the discovery of a new species of Ebola virus, Bundibugyo Ebola virus (BEBOV). Between 2001 and 2005, Gabon and Republic of Congo (RC) were hit by five ZEBOV outbreaks [12-15]; in 2003 again Republic of Congo was affected. Bundibugyo Ebola virus (BEBOV) was discovered in 2007 in Uganda and led to a large outbreak with 116 cases and 30 deaths (fatality rate 26%). In

2008 DRC reported 14 deaths out of 32 cases due to Zaire ebola virus species. In 2012 it further reported 29 deaths out of 57 cases in the same area due to Bundibugyo ebola virus. Further in the years 2011- 2012 Uganda reported 4 deaths out of 7 cases due to Sudan Ebola virus species.

The current outbreak in West Africa (first cases notified in March 2014), is the largest and most complex Ebola outbreak since the Ebola virus was first discovered in 1976. There have been more cases and deaths in this outbreak than all others combined. It has also spread between countries starting in Guinea then spreading across land borders to Sierra Leone and Liberia, by air (1 traveler only) to Nigeria, and by land (1 traveler) to Senegal. The virus causing the 2014 West African outbreak belongs to the Zaire species. Ebola deaths up to 30 September 2014 were 3439 (2,069 in Liberia, 739 in Guinea and 623 in Sierra Leone).

## PATHOGENESIS OF EBOLA VIRUS

The Ebola virus Glycoprotein (GP) is synthesized in a secreted (sGP) or full-length transmembrane form, and each gene product has distinct biochemical and biological properties. GP appears to form a trimeric complex [16] and binds preferentially to endothelial cells, whereas sGP does not [17]. Host immune responses to Ebola virus and cell damage due to direct infection of monocytes and macrophages cause the release of cytokines associated with inflammation and fever. Infection of endothelial cells also induces a cytopathic effect and damage to the endothelial barrier that together with cytokine effects leads to the loss of vascular integrity. Transient expression of Ebola virus GP in human umbilical vein endothelial cells or 293T cells causes a reduction of specific integrins (primary molecules responsible for cell adhesion to the extracellular matrix) and immune molecules on the cell surface. The presence of viral particles and cell damage resulting from budding causes the release of chemical signals (to be specific, TNF- $\alpha$ , IL-6, IL-8, etc.), which are the signaling molecules for fever and inflammation.

The cytopathic effect, from infection in the endothelial cells, results in a loss of vascular integrity. This loss in vascular integrity is furthered with synthesis of GP, which reduces specific integrins responsible for cell adhesion to the inter-cellular structure and damage to the liver, which leads to improper clotting. Cytokine dysregulation and virus infection may synergize at the endothelial surface promoting hemorrhage and vasomotor collapse (Figure 3) [18].

**Transmission patterns and epidemiology of ebola virus:**

With the exception of the recognized outbreaks, the epidemiology of Ebola virus infections in humans is unknown [19]. After infection from the initial source, infection is spread by person-to-person contact through infected bodily fluids such as blood. Other body fluids with ebola virus include saliva, mucus, vomit, feces, sweat, tears, breast milk, urine, and semen. Entry points include the nose, mouth, eyes, or open wounds, cuts and abrasions. The potential for widespread EVD (Ebola virus disease) infections is considered low as the disease is only spread by direct contact with the secretions from someone who is showing signs of infection. The symptoms limit a person's ability to spread the disease as they are often too sick to travel. Because dead bodies are still infectious, traditional burial rituals may spread the disease. Nearly two thirds of the cases of Ebola in Guinea during the 2014 outbreak are believed to be due to burial practices. Semen may be infectious in survivors for up to 7 weeks. It is not entirely clear how an outbreak is initially started. The initial infection is believed to occur after ebola virus is transmitted to a human by contact with an infected animal's body fluids. Healthcare facilities can be a major source of virus transmission. Improper barrier nursing techniques as well as the reuse of infected needles help spread the virus into the community and to the healthcare workers. It may be spread by infected animals. Ebola is not spread through the air or by water, or in general, by food. However, in Africa, Ebola may be spread as a result of handling bush meat (wild animals hunted for food) and contact with infected bats. There is no evidence that mosquitoes or other insects can transmit Ebola virus. Only mammals (for example, humans, bats, monkeys, and apes) have shown the ability to become infected with and spread Ebola virus. For example, in the 1995 Zaire ebolavirus outbreak in Zaire, one-fourth of the cases were among healthcare workers [19]. During outbreaks of Ebola, the disease can spread quickly within healthcare settings (such as a clinic or hospital).

**Clinical presentation and symptoms:** The incubation period of EHF is between 2 and 21 days [20]. Symptoms manifest abruptly and are often non-specific flu-like and may include chills, fever, myalgia, and malaise followed by lethargy, nausea, vomiting, abdominal pain, anorexia, diarrhea, coughing, headache, and hypotension [20]. Hemorrhaging occurs in less than 50 percent of patients.

**Symptoms of Ebola;** Early on, Ebola can feel like the flu or other illnesses. Symptoms show up 2 to 21 days after infection and usually include:

- High fever

- Headache
- Joint and muscle aches
- Sore throat
- Weakness
- Stomach pain
- Lack of appetite

As the disease gets worse, it causes bleeding inside the body, as well as from the eyes, ears, and nose [21]. Over time, symptoms become increasingly severe and may include:

- Nausea and vomiting
- Diarrhea (may be bloody)
- Red eyes
- Raised rash
- Chest pain and cough
- Severe weight loss
- Bleeding, usually from the eyes, and bruising (people near death may bleed from other orifices, such as ears, nose and rectum)
- Internal bleeding [24]

**DIAGNOSIS**

It can be difficult to distinguish EVD from other infectious diseases such as malaria, typhoid fever and meningitis. Samples from patients are an extreme biohazard risk; laboratory testing on non-inactivated samples should be conducted under maximum biological containment conditions (Table 1) [22, 23].

**TREATMENT**

No FDA-approved vaccine or medicine (e.g., antiviral drug) is available for Ebola. Symptoms of Ebola are treated as they appear. The following basic interventions, when used early can significantly improve the chances of survival:

- Providing intravenous fluids (IV) and balancing electrolytes (body salts)
- Maintaining oxygen status and blood pressure
- Treating other infections that develop
- Replacing lost blood
- Providing fluids [24]

Experimental vaccines and treatments for Ebola are under development, but they have not yet been fully tested for safety or effectiveness. Recovery from Ebola depends on good supportive care and the patient's immune response. People who recover from Ebola infection develop antibodies that last for at least 10 years, possibly longer. It isn't known if people who recover are immune for life or if they can become infected with a different species of Ebola. Some people who have recovered from Ebola have developed long-term complications, such as joint and vision problems.

**New Ebola MEDICATIONS IN development**

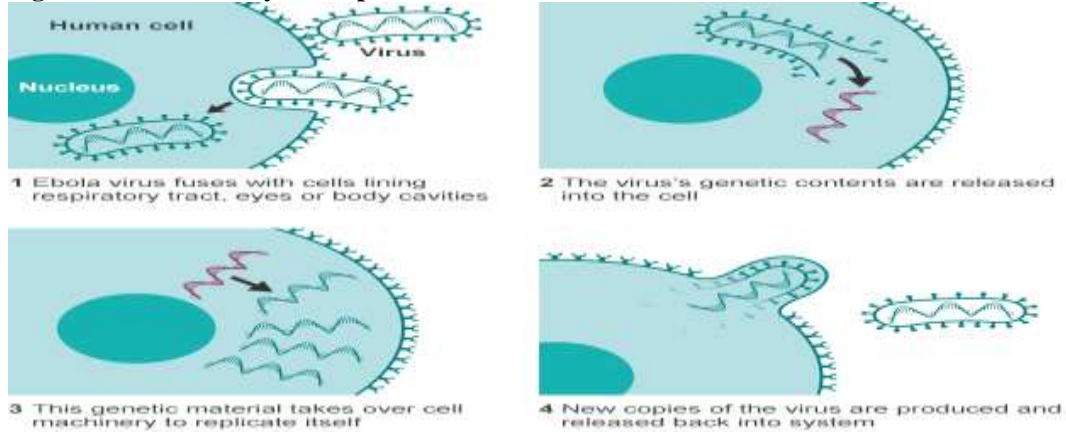
The U.S. Food and Drug Administration have not approved any treatments for Ebola. The drug is called ZMapp, developed in early 2014 and it's

made by Mapp Biopharmaceutical Inc. It's an experimental, antibody-based medication, explains Pigott, but it has not been tested in human trials for effectiveness.

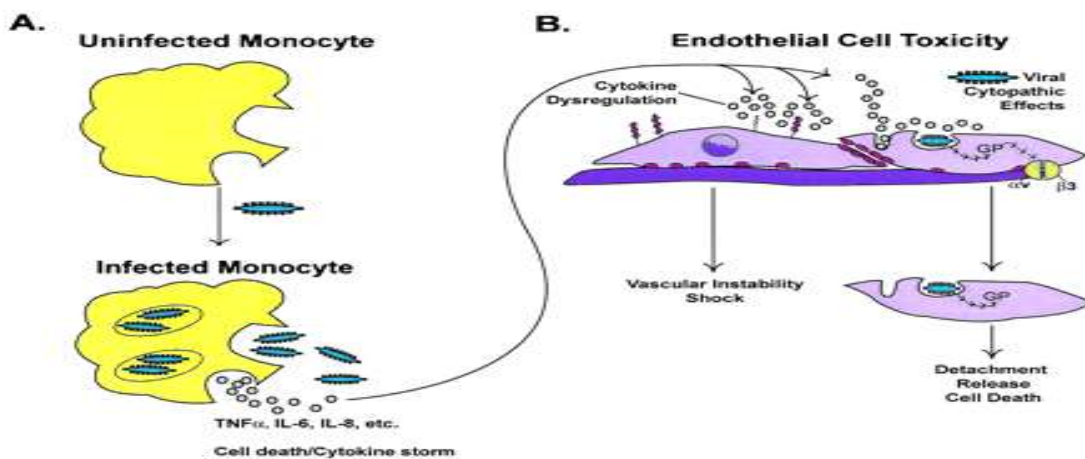
**Figure 1: Electron microscopy of Ebola virus**



**Figure 2: mode of entry and replication of Ebola virus in host**



**Figure 3: pathogenesis of Ebola virus**



**TABLE 1: Diagnostic tests for Ebola Detection**

Timeline of Infection	Diagnostic tests available
Within a few days after symptoms begin	- Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing - IgM ELISA - Polymerase chain reaction (PCR) - Virus isolation
Later in disease course or after recovery	- IgM and IgG antibodies
Retrospectively in deceased patients	- Immunohistochemistry testing - PCR - Virus isolation

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