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Review Article

Ebola Haemorrhagic Fever: An Overview

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ABSTRACT

Ebola virus disease is a rare but severe, often fatal illness in humans. Fruit bats are the natural reservoirs of Ebola virus, and it is transmitted to humans from wild animals and spreads between humans. Ebola virus is a class A bioterrorism agent, known to cause highly lethal haemorrhagic fever. Clinical symptoms include fever, myalgia, headache followed by vomiting, diarrhea, hemorrhagic rash, bleeding, and multi-organ failure. Vaccines to protect against Ebola have been developed and used to control the spread of Ebola virus disease. Treatment is mainly early supportive care with rehydration and symptomatic treatment. Ebola virus is a neglected pathogen and the knowledge and scientific information on Ebola virus disease is relatively limited and received little attention. Better understanding of ebolavirus disease mechanisms is needed to guide development of drugs, vaccines, and treatment strategies. Hence this comprehensive review on Ebola virus is undertaken to provide an overview of its transmission, pathogenesis, clinical symptoms, differential diagnosis, laboratory diagnosis, treatment, vaccines and preventive aspects and to highlight its importance, and impact on public health and further research.

Keywords: Bats, Ebola virus, Hemorrhagic fever, Infectious disease.

INTRODUCTION

Ebola virus disease, formerly known as Ebola haemorrhagic fever, is an acute, severe illness which is often fatal if untreated. The virus family Filoviridae includes 3 genera: *Cuveavirus*, *Marburgvirus*, and *Ebolavirus*. There are six species that have been identified in the genus Ebolavirus: Zaire, Bundibugyo, Sudan, Reston, Tai Forest, and Bombali. The first 3, Zaire Ebolavirus, Bundibugyo Ebolavirus, and Sudan Ebolavirus have been associated with large outbreaks in Africa. The virus causing the 2013-2016 West African outbreak belongs to the Zaire species. Filovioruses replicate in the cytoplasm of host cells. Ebola virus is a neglected pathogen and the knowledge and scientific information on Ebola virus disease is relatively limited and received little attention. Hence this comprehensive review

on Ebola virus is undertaken to provide an overview of its transmission, pathogenesis, clinical symptoms, differential diagnosis, laboratory diagnosis, treatment, vaccines and preventive aspects and to highlight its importance, and impact on public health and further research [1-3].

Epidemiology

Ebola virus disease first appeared in 1976 in two simultaneous outbreaks, one in Zaire (Zaire Ebola virus) and Sudan (Sudan Ebola virus), and involved 318 and 284 patients, respectively. So far, 29 Ebola virus outbreaks have been reported, involving small numbers of patients [4]. In 2000-2001, there was a relatively large outbreak with 425 patients in Gulu district, Uganda with Sudan Ebola virus [4-6].

The 2013-2016 outbreak in West Africa was the largest multi-country outbreak in the history by Zaire Ebola virus with 28,616 cases and 11,310 deaths. The outbreak started in Guinea and then spread to Sierra Leone and Liberia [6]. On August 8th, 2014 the WHO declared this outbreak a Public Health Emergency of International Concern [7]. A few cases have also been reported in countries outside of West Africa, all related to International travelers who were exposed in the most affected regions and later showed symptoms of Ebola fever after reaching their destinations [8].

Democratic Republic of Congo had two genetically distinct Ebola virus outbreaks of Zaire Ebola virus; the first was in Equator province in May 2018, and the second was in Ituri and North Kivu provinces in August 2018, one week after the end of the Equator outbreak. This was the tenth outbreak in Democratic Republic of Congo/Zaire with 3317 confirmed cases; 29% (1002 cases) were children under 18 years of age. There were 2280 deaths, with a case fatality rate of 66% [9-12]. The eleventh outbreak in Democratic Republic of Congo with Zaire Ebola ended on 18 November, 2020 [13].

Structure of Virus

Ebola virus (EBOV) is characteristically long, thread like, filamentous or tubular, and measures 800-1000 nm. Ebola virion contains viral envelope, matrix and nucleocapsid components [1]. The viral envelope carries 7-10 nm long glycoprotein spikes (virally encoded) projecting from its lipid bilayer surface. Viral proteins VP40 and VP24 are located between the envelope and nucleocapsid in the matrix space.

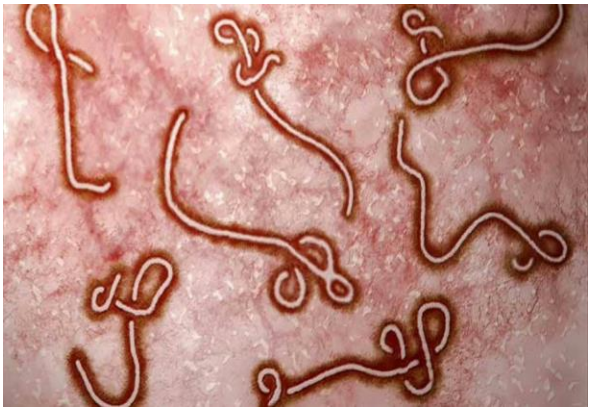

Figure 1: Ebola virus [14]

At the center of the virion is the nucleocapsid, which is composed of a series of viral proteins, attached to 18-19 kb linear, negative sense RNA genome [3]. The RNA is helically wound and complexed with the nucleoprotein (NP), polymerase cofactor viral protein (VP35), transcription activator (VP30), and viral RNA-dependent RNA polymerase (L). The helix has a diameter of 80 nm and contains a central channel of 20-30 nm. The prototype Ebola virus, variant Mayinga (EBOV/May), was named for

Mayinga N'Seka, a nurse who died during the 1976 Zaire outbreak [14,15].

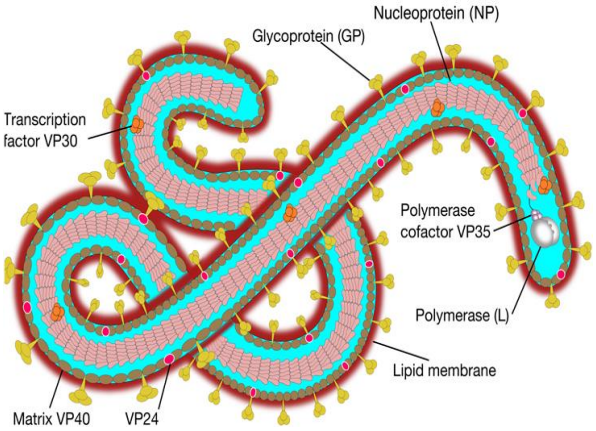

Figure 2. Ebolavirus structure [15]

Transmission

Ebola virus is a zoonotic pathogen. The virus is harbored in fruit bats, gorillas, monkeys, forest antelope, chimpanzees, and porcupines [16]. Ebola is introduced into the human population through close contact with the blood, secretions, organs or other bodily fluids of these infected animals.

Ebola then spreads directly through human-to-human transmission via direct contact (through broken skin or mucus membranes) with the blood, secretions, organs or other bodily fluids (tears, feces, urine, vomit etc.) of infected people, or indirectly from surfaces and materials (e.g. bedding, clothing, surgical equipment or a needle) contaminated with these fluids. People remain infectious as long as their blood and body fluids, including semen and breast milk, contain the virus. Men who have recovered from the disease can still transmit the virus through their semen for up to seven weeks after recovery from illness [17,18]. Health care workers have frequently been infected while treating patients with suspected or confirmed Ebola virus disease [19]. Ebola virus infection is most fatal, and

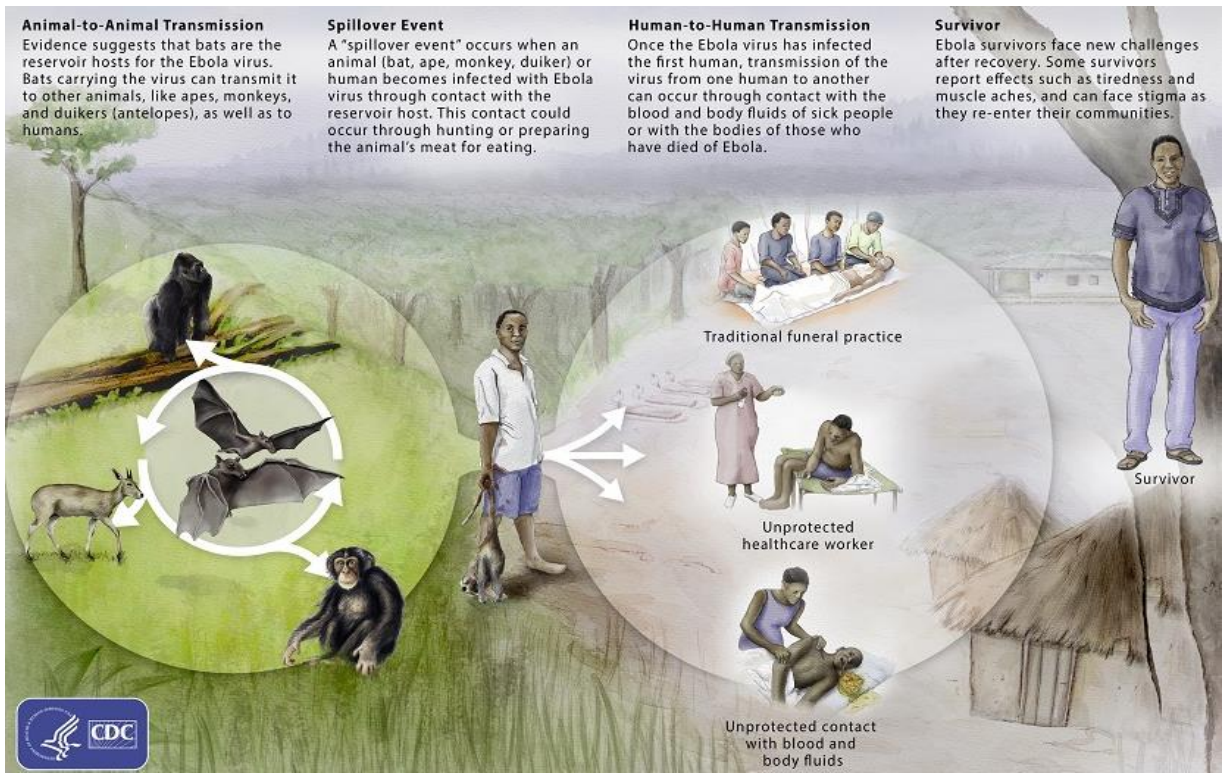

Figure 3. Ebola virus ecology and transmission (CDC) [18]

therefore, Ebolavirus is identified as a bio-safety level 4 pathogens and CDC category A agents of bioterrorism [13].

Pathogenesis

Ebola virus has a predilection to infect various cells of immune system (dendritic cells, monocytes, macrophages), endothelial and epithelial cells, hepatocytes, and fibroblasts. Following viral inoculation onto skin, Ebola virus targets dendritic cells, monocytes, and macrophages [1].

These virus-infected cells then travel via lymphatic vessels to regional lymph nodes causing lymphadenopathy, where virus replication and dissemination to liver and spleen occur through blood circulation and induce an inflammatory response, with release of cytokines which may cause intravascular coagulation and multiple organ dysfunction associated with both early immune evasion and subsequent immune damage. In the absence of adequate supportive care, these processes commonly result in multiple organ failure and death within about 10 days of symptom onset in humans [20,23].

Clinical Symptoms

The incubation period, that is, the time interval from infection with the virus to onset of symptoms is two to 21 days. The initial symptoms are the sudden onset of high fever, fatigue, muscle pain, headache, and stomach pain. There may also be sore throat, hiccups and red and itch eyes. This is followed by vomiting, diarrhea, rash, and bleeding problems that include bloody nose (epistaxis), spitting up blood from the lungs (hemoptysis), vomiting blood from the stomach (hematemesis) and bloody eyes (conjunctival hemorrhages), symptoms of impaired kidney and liver function. Then finally come chest pain, shock and death. Laboratory findings include low WBC and platelet counts and elevated liver enzymes [23-26].

A protein on the surface of the virus has been discovered that is responsible for the severe internal bleeding (the death-dealing feature of the disease). The protein attacks and destroys the endothelial cells lining blood vessels, causing the vessels to leak and bleed, contributing to vascular permeability and intravascular coagulation. The mortality rate varies from 25% to 90% and the average mortality rate is around 50% [25, 26].

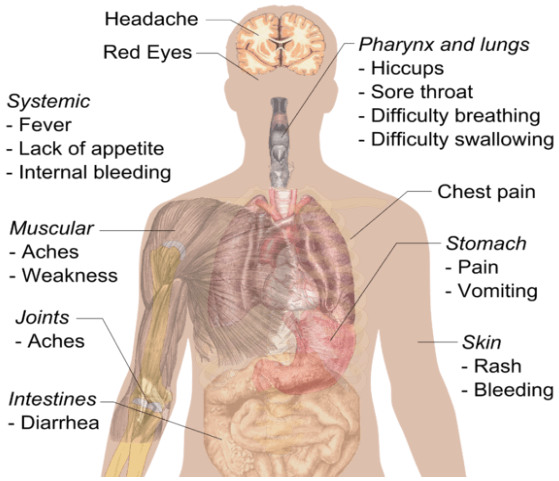

Figure 4. Clinical symptoms of Ebola virus disease [25]

Diagnosis

Samples from patients are extreme biohazard risk. The preferred samples for diagnosis include i) whole blood collected in EDTA from live suspected patients, ii) oral fluid specimen stored in universal transport medium collected from deceased patients or when blood collection is not possible. Ebola virus infection can be diagnosed by using the diagnostic tests such as RT-PCR; serological demonstration of antibodies in patient serum by ELISA, immunofluorescence, serum neutralization tests; detection of viral antigen

by ELISA and immunofluorescence; electron microscopy; and virus isolation by cell culture [27,28].

Differential Diagnosis

It can be difficult to distinguish Ebola virus disease from other infectious diseases such as malaria, influenza, typhoid fever, leptospirosis, relapsing fever, meningitis, Marburg virus infection, Crimean Congo hemorrhagic fever, Lassa fever, Rift valley fever, yellow fever, Rickettsial infections, Dengue fever, chikungunya, and Measles. Many symptoms of pregnancy and Ebola virus disease are also quite similar [29].

Treatment

There is no proven treatment available for Ebola virus disease. Therefore, treatment for Ebola virus disease consists of early supportive care which often includes administering oral or intravenous (IV) fluids and monitoring and maintaining appropriate electrolyte, oxygen, and blood pressure levels, and treatment of specific symptoms.

WHO has made strong recommendations for the use of two monoclonal antibody treatments in treating Ebola: mAb114 (Ansuvimab; Ebanga) and REGN-EB3 (Inmazeb) approved by the US FDA in late 2020, administered intravenously as a single infusion. These monoclonal antibodies target the glycoprotein on the surface of Ebola virus, preventing virus attachment and entry of virus into host cell [30-32].

Vaccines

The Ervebo vaccine was approved in December 2020 by the US FDA for used in individuals 18 years of age and older except for pregnant and breastfeeding women for protection against Ebola virus disease caused by Zaire Ebola virus. It is a recombinant vesicular stomatitis virus-Zaire Ebola virus vaccine (rVSV-ZEBOV, now known as Ervebo) [33]. Another vaccine the adenovirus 26 vectored glycoprotein/MVA-BN (Ad26.ZEBOV/MVA-BN) was also given to large number of individuals [34].

Prevention and Control

Good outbreak control relies on preventing transmission and spread of the virus by early case detection, contact tracing, isolation of infected persons, surveillance, clinical management, safe burial and social mobilization. Health care workers should always take standard precautions when caring for patients. These include basic hand hygiene, respiratory hygiene, using personal protective equipment, and environmental cleaning and disinfection [35,36].

Conclusion

Ebola hemorrhagic fever is a deadly viral infection that cause internal and external bleeding leading to multi-organ dysfunction, can be fatal. Early supportive care with rehydration and symptomatic treatment may improve survival. WHO has made strong recommendations for the use of two monoclonal antibody treatments in treating Ebola: mAb114 (Ansuvimab; Ebanga) and REGN-EB3 (Inmazeb).

Ebola virus disease poses a global public health threat due to multiple disease outbreaks in the last two decades. Though there are some advances in the development of Ebola virus vaccine and anti-Ebola virus drugs, further research is required to develop effective drugs and treatment strategies, vaccines, and specific diagnostic tests, and to understand immunological mechanisms of pathogenesis.

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Conflict of interest

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