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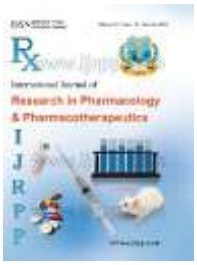

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Ebola virus disease - A comprehensive review

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ABSTRACT

Ebola virus disease (EVD) is caused by infection with Ebola virus. Ebola virus disease first appeared in 1976 in 2 simultaneous outbreaks, one in Nzara, Sudan, and the other in Yambuku, Democratic Republic of Congo. The latter occurred in a village near the Ebola River, from which the disease takes its name. Fruit bats are considered possible natural hosts for Ebola virus. Ebola virus enters the patient through mucous membranes, breaks in the skin, or parenterally. EVD is often characterized by the sudden onset of fever, intense weakness, muscle pain, headache and sore throat. No FDA-approved vaccine or medicine is available for Ebola. Several vaccines are being developed and the two most advanced vaccines identified based on recombinant vesicular stomatitis virus expressing an Ebola virus protein (VSV-EBOV) and recombinant chimpanzee adenovirus expressing an Ebola virus protein (ChAd-EBOV) – are currently being tested in humans for safety and efficacy and trials were started. Scientists are working on variety of vaccines and antiviral drugs for Ebola viruses. Increasing public awareness and prevention of Ebola virus disease (EVD) spreading are the presently needed essentials for the community.

Keywords: Ebola virus disease (EVD), mucous membranes, Niemann–Pick C1 (NPC1), TIM-1 (aka HAVCR1), ELISA, Ebola virus protein (VSV-EBOV), phospho-morpholino oligonucleotides (PMOs)

INTRODUCTION

Ebola virus disease (EVD) 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 five identified subtypes of Ebola virus. Four of the five have caused disease in humans: Ebola-Zaire, Ebola-Sudan, Ebola-Ivory Coast and Ebola-Bundibugyo. The fifth, Ebola-Reston, has caused disease in nonhuman primates, but not in humans. The exact origin, locations, and natural habitat (known as the "natural reservoir") of Ebola virus remain unknown. However, on the basis of available evidence and the nature of similar viruses, researchers believe that the virus is zoonotic (animal-borne) with four of the five subtypes occurring 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 infected cynomolgous monkeys that were imported to the United States and Italy from the Philippines. The virus is not known to be native to other continents, such as North America[1].

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The EBOV genome is a single-stranded RNA approximately 19,000 nucleotides long. It encodes seven structural proteins: nucleoprotein (NP), polymerase cofactor (VP35), (VP40), GP, transcription activator (VP30), VP24, and RNA polymerase (L)[2]

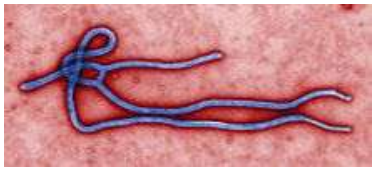

Fig 1: Electron micrograph of an Ebola virus

EPIDEMIOLOGY

Ebola virus disease (EVD) first appeared in 1976 in 2 simultaneous outbreaks, one in Nzara, Sudan, and the other in Yambuku, Democratic Republic of Congo. The latter occurred in a village near the Ebola River, from which the disease takes its name[3].

An outbreak of haemorrhagic fever due to EVD in Guinea and Liberia, West Africa, with onset in early February 2014, is ongoing. The first cases were reported from the forested region of south-eastern Guinea in Guéckédou prefecture near the border with Liberia and Sierra Leone. The Ebola viral aetiology was confirmed on 22 March 2014 by the National Reference Centre for Viral Haemorrhagic Fevers (Institute Pasteur, INSERM BSL4 laboratory, Lyon, France). Sequencing of part of the outbreak virus L-gene has shown that it is 98% homologous with an EBOV last reported in 2009 in Kasai-Occidental Province of the Democratic Republic of Congo. This ebolavirus species has been associated with a high case-fatality during previous outbreaks.

As of 7 April 2014, the Ministry of Health of Guinea has reported 151 clinically compatible cases of EVD, including 95 deaths. Cases have been reported from Conakry, Guéckédou, Macenta, Kissidougou, and from Dabola and Djingaraye prefectures. Fifty-four cases have tested positive for Ebola virus by PCR. At least 14 of the cases in Guinea have been healthcare workers, and eight of them have died, which indicates the need to further strengthen health facility-based infection prevention and control. Thirty-three patients had recovered after palliative treatment and were discharged from the isolation centres (Guéckédou 16, Macenta 9, Conakry 5, and Kissidougou 3). As of 7 April, 623 contacts are under follow-up[4].

As of August 9, 2014, according to WHO, a total of 1,848 cases and 1,013 deaths had been reported across the four affected countries of Guinea, Liberia, Sierra Leone and Nigeria. This is the largest outbreak of Ebola Virus Disease (EVD) ever documented and the first recorded in West Africa. The death rate in some Ebola outbreaks can be as high as 90%, but in

this outbreak it is currently around 55%-60%[5]. As of 5 September 2014, 540 cases had been reported, with an apparent overall case-fatality ratio of about 50%; many more cases have gone unrecorded. The outbreaks in some sites seem to be expanding at an exponential rate[6].

SOURCE

In Africa, fruit bats, particularly species of the genera Hypsignathus monstrosus, Epomops franqueti, and Myonycteris torquata, are considered possible natural hosts for Ebola virus. As a result, the geographic distribution of Ebola viruses may overlap with the range of the fruit bats.

Although non-human primates have been a source of infection for humans, they are not thought to be the reservoir, but are an accidental host like human beings. Since 1994, Ebola outbreaks from the EBOV and TAFV (Tai Forest virus species) species have been observed in chimpanzees and gorillas.

TRANSMISSION

Ebola is introduced into the human population through close contact with the blood, secretions, organs, or other bodily fluids of infected animals. In Africa, infection has been documented through the handling of infected chimpanzees, gorillas, fruit bats, monkeys, forest antelope, and porcupines found ill or dead or in the rainforest.

Ebola then spreads in the community through human-to-human transmission, with infection resulting from direct contact through broken skin or mucous membranes with the blood, secretions, organs, or other body fluids of infected, symptomatic persons, and indirect contact with environments contaminated with such fluids. Transmission does not occur during the incubation period and only occurs once an infected person presents with symptoms. Burial ceremonies in which mourners have direct contact with the body of the deceased person can also play a role in the transmission of Ebola. Men who have recovered from the disease can still transmit the virus through their semen for up to 3 months after recovery.

Health-care workers have frequently been infected while treating symptomatic patients infected with Ebola virus disease. This may occur through close contact with patients when infection control precautions are not strictly practiced, including basic measures – such as hand hygiene – that should be applied even before a patient is suspected of being infected with Ebola virus disease[7].

PATHOGENESIS

Ebola virus enters the patient through mucous membranes, breaks in the skin, or parenterally and infects many cell types, including monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes, adrenal cortical cells and epithelial cells. The incubation period may be related to the infection route. Ebola virus migrates from the initial infection site to regional lymph nodes and subsequently to the liver, spleen and adrenal gland. Although not infected by Ebola virus, lymphocytes undergo apoptosis resulting in decreased lymphocyte counts. Hepatocellular necrosis occurs and is associated with dysregulation of clotting factors and subsequent coagulopathy. Adrenocortical necrosis also can be found and is associated with hypotension and impaired steroid synthesis. Ebola virus appears to trigger a release of pro-inflammatory cytokines with subsequent vascular leak and impairment of clotting ultimately resulting in multi-organ failure and shock[8].

ENTRY

There are two candidates for host cell entry proteins. The first is the host-encoded Niemann–Pick C1 (NPC1), a cholesterol transporter protein, appears to be essential for entry of Ebola virions into the host cell, and for its ultimate replication[9, 10]. In one study, mice that were heterozygous for NPC1 were shown to be protected from lethal challenge with mouse-adapted Ebola virus[9]. In another study, small molecules were shown to inhibit Ebola virus infection by preventing viral envelope glycoprotein (GP) from binding to NPC1[10, 11]. Hence, NPC1 was shown to be critical to entry of this filovirus, because it mediates infection by binding directly to viral GP[10]. When cells from Niemann Pick Type C patients lacking this transporter were exposed to Ebola virus in the laboratory, the cells survived and appeared impervious to the virus, further indicating that Ebola relies on NPC1 to enter cells; mutations in the NPC1 gene in humans were conjectured as a possible mode

to make some individuals resistant to this deadly viral disease.

The same studies described similar results regarding NPC1's role in virus entry for Marburg virus, a related filovirus. A further study has also presented evidence that NPC1 is critical receptor mediating Ebola infection via its direct binding to the viral GP, and that it is the second "lysosomal" domain of NPC1 that mediates this binding[12].

The second candidate is TIM-1 (aka HAVCR1).TIM-1 was shown to bind to the receptor binding domain of the EBOV glycoprotein, to increase the receptivity of Vero cells. Silencing its effect with siRNA prevented infection of Vero cells. TIM1 is expressed in tissues known to be seriously impacted by EBOV lysis (trachea, cornea, and conjunctiva). A monoclonal antibody against the IgV domain of TIM-1, ARD5, blocked EBOV binding and infection. Together, these studies suggest NPC1 and TIM-1 may be potential therapeutic targets for an Ebola anti-viral drug and as a basis for a rapid field diagnostic assay[13].

REPLICATION

Being unicellular, viruses do not grow through cell division; instead, they use the machinery and metabolism of a host cell to produce multiple copies of themselves, and they assemble in the cell[14].

The virus attaches to host receptors through the glycoprotein (GP) surface peplomer and is endocytosed into macropinosomes in the host cell. Viral membrane fuses with vesicle membrane, nucleocapsid is released into the cytoplasm. Encapsidated, negative-sense genomic ssRNA is used as a template for the synthesis (3' –5') of polyadenylated, monocistronic mRNAs. Using the host cell's machinery translation of the mRNA into viral proteins occurs. Viral proteins are processed, glycoprotein precursor (GP0) is cleaved to GP1 and GP2, which are heavily glycosylated. These two molecules assemble, first into heterodimers, and then into trimers to give the surface peplomers. Secreted glycoprotein (sGP) precursor is cleaved to sGP and delta peptide, both of which are released from the cell. As viral protein levels rise, a switch occurs from translation to replication. Using the negative-sense genomic RNA as a template, a complementary +ssRNA is synthesized; this is then used as a template for the synthesis of new genomic (-)ssRNA, which is rapidly encapsidated. The newly formed nucleocapsids and envelope proteins associate at the host cell's plasma membrane; budding occurs, destroying the cell[15].

SIGNS AND SYMPTOMS

EVD is a severe acute viral illness often characterized by the sudden onset of fever (greater than 38.6°C or 101.5°F), intense weakness, muscle pain, headache and sore throat. This is followed by vomiting, diarrhoea, rash, impaired kidney and liver function, and in some cases, both internal and external bleeding. Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes.

People are infectious as long as their blood and secretions contain the virus. Ebola virus was isolated from semen 61 days after onset of illness in a man who was infected in a laboratory.

The incubation period is 2 to 21 days[16]. Recovery from Ebola depends on good supportive clinical care and the patient's immune response. People who recover from Ebola infection develop antibodies that last for at least 10 years[17].

EXPOSURE RISK LEVELS

Table 1: Levels of risk of transmission of Ebola virus according to type of contact with an infected patient

Risk level	Type of contact
Very low or no recognized risk	Casual contact with a feverish, ambulant, self-caring patient. Examples: sharing a sitting area or public transportation; receptionist tasks.
Low risk	Close face-to-face contact with a feverish and ambulant patient. Example: physical examination, measuring temperature and blood pressures.

Moderate risk	Close face-to-face contact without appropriate personal protective equipment (including eye protection) with a patient who is coughing or vomiting, has nosebleeds or who has diarrhoea.
High risk	Percutaneous, needle stick or mucosal exposure to virus-contaminated blood, bodily fluids, tissues or laboratory specimens in severely ill or known positive patients

A literature indicates low risk of transmission in the early phase of symptomatic patients (prodromal phase around seven days) [18]. Risk of transmission may increase with transition to later stages of the disease with increasing viral titers[19]. In a household study, secondary transmission only took place if direct physical contact occurred. No transmission was reported without direct contact [20]. During an outbreak of Sudan Ebola virus in 2000 in Uganda, the most important risk factor was direct repeated contact with a sick person's bodily fluids during the provision of care. The risk was higher when exposure took place during the late stages of the disease. Simple physical contact with a sick person appeared not to be sufficient for contracting Ebola infection. Transmission through fomites heavily contaminated with bodily fluids is possible[19].

DIAGNOSIS

Diagnosing Ebola in a person who has been infected for only a few days is difficult because the early symptoms, such as fever, are not specific to Ebola infection and are seen often in patients with more commonly occurring diseases, such as malaria and typhoid fever. However, if a person has symptoms of Ebola and had contact with blood or body fluids of a person sick with Ebola, contact with objects that have been contaminated with blood or body fluids of a person sick with Ebola, or contact with an infected animal, the patient should be isolated and public health professionals notified. Samples from the patient can then be collected and tested to confirm infection[1].

Table 2: Laboratory tests used in diagnosis:

Infection Timeline	Diagnostic tests
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

PREVENTION

There is no FDA-approved vaccine available for Ebola.

Travel to or are in an area affected by an Ebola outbreak, do the following for the prevention:

1. Practice careful hygiene. For example, wash hands with soap and water or an alcohol-based hand sanitizer and avoid contact with blood and body fluids.
2. Do not handle items that may have come in contact with an infected person's blood or body fluids (such as clothes, bedding, needles, and medical equipment).
3. Avoid funeral or burial rituals that require handling the body of someone who has died from Ebola.
4. Avoid contact with bats and nonhuman primates or blood, fluids, and raw meat prepared from these animals.
5. Avoid hospitals where Ebola patients are being treated.
6. After return, monitor your health for 21 days and seek medical care immediately if Ebola symptoms develop.

Healthcare workers who may be exposed to people with Ebola may follow these steps:

1. Wear protective clothing, including masks, gloves, gowns, and eye protection.
2. Practice proper infection control and sterilization measures.
3. Isolate patients with Ebola from other patients.
4. Avoid direct contact with the bodies of people who have died from Ebola.
5. Notify health officials if you have had direct contact with the blood or body fluids, such as but not limited to, feces, saliva, urine, vomit, and semen of a person who is sick with Ebola. The virus can enter the body through broken skin or unprotected mucous membranes in, for example, the eyes, nose, or mouth[21].

TREATMENT

No FDA-approved vaccine or medicine (e.g., antiviral drug) is available for Ebola. Experimental vaccines and treatments for Ebola are under development, but they have not yet been fully tested for safety or effectiveness[17].

Symptoms of Ebola are treated as they appear. The following basic interventions, when used early, can significantly improve the chances of survival:

1. Providing intravenous(IV) fluids and balancing electrolytes (body salts)
2. Maintaining oxygen status and blood pressure
3. Treating other infections if they occur

Timely treatment of Ebola is important but challenging since the disease is difficult to diagnose clinically in the early stages of infection. Because early symptoms such as headache and fever are not specific to Ebola viruses, cases of Ebola may be initially misdiagnosed.

However, if a person has symptoms of Ebola and had contact with blood or body fluids of a person sick with Ebola, contact with objects that have been contaminated with blood or body fluids of a person sick with Ebola, or contact with an infected animal, the patient should be isolated. Supportive therapy can continue with proper protective clothing until samples from the patient are tested to confirm infection.

Experimental treatment has been tested and proven effective in some animals but has not yet been evaluated in humans[1].

Several vaccines are being developed and the two most advanced vaccines identified based on recombinant vesicular stomatitis virus expressing an Ebola virus protein (VSV-EBOV) and recombinant chimpanzee adenovirus expressing an Ebola virus protein (ChAd-EBOV) – are currently being tested in humans for safety and efficacy in the United States of America and trials were started in Africa and Europe.

A cocktail of monoclonal antibodies against Ebola virus (Zmapp) has already been used compassionately in a few patients with Ebola, however the number is too small to enable any assessment of safety or efficacy and it will be several months before more products is available. Other immunoglobulins, derived from immunized humans or animals may have therapeutic value. Such products, while being developed, will not be available for at least 6 months and will need to undergo testing for efficacy in non-human primates.

Other potential therapeutics under development include: novel nucleotide analogues and other small antiviral molecule agents such as favipiravir, BCX4430, brincidofovir; RNA-based drugs such as small-inhibitory RNA (siRNA) and phospho-morpholino oligonucleotides (PMOs); and drugs that affect coagulation such as recombinant nematode anti-coagulant protein or recombinant activated protein C. Some of these have demonstrated safety in humans and efficacy in animal models, however clinical evaluation will be required to determine whether they are efficacious in human Ebola infections and whether they are safe at the doses required. In addition, supplies for some of the most advanced products are limited to just a few tens or hundreds of doses.

In addition to these novel products, there are also several existing medicines that have been approved for treatment of other diseases and conditions but which may be re-purposed for EVD. These include the antiviral favipiravir, immunomodulatory drugs, such as interferons, and estrogen receptor modulators. While some efficacy has been demonstrated in small animal models with these drugs and they have a history of use in humans, it is

not known if they will be safe or efficacious in EVD patients[6].

Nucleoside analogue inhibitors of the cell-encoded enzyme S-adenosylhomocysteine hydrolase (SAH) have been shown to inhibit Zaire ebolavirus replication in adult BALB/c mice infected with mouse-adapted Ebola virus[22]. In rhesus macaques infected with a lethal dose of Ebola virus, treatment with interferon beta early after exposure led to a significant increase in survival time, though it did not reduce mortality significantly[23].

CONCLUSION

Scientists are working on a variety of vaccines and antiviral drugs that would protect people from Ebola or Marburg viruses. Multiple products are in the development pipeline. Some of the results have been promising, but further testing is needed. Increasing public awareness and prevention of Ebola virus disease (EVD) spreading are the presently needed essentials for the community. As several clinical studies are under process worldwide, we can expect the development of potent and safe drugs for the treatment of Ebola virus disease (EVD).

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