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Ebola Virus Infection: Life Cycle, Prevention, Controland Its Treatment Opportunities

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ABSTRACT

Ebola is a serious and deadly virus transmitted by animals and humans. It is come under the Filoviridae family. It causes very high fever, which lead to bleeding in the body (inside and outside), thereby also called as hemorrhagic fever. Ebola is further classified into subtypes (Bundibugyo, Reston, Sudan, Taï Forest, Zaire) according to location where they were identified.This virus is transmitted by animals (primates only) to human, therefore it is called as zoonotic virus. Human to human transfer is also found in Ebola virus infection.There is no drug is approved by US-FDA till date for this disease.

In this review, we summarized the pathogenesis of infection as well as importance of different proteins in Ebola life cycle. In addition, treatment, control and management of the Ebola disease are also highlighted. Indeed, in recent advances about the structure and biology of Ebola virus and itscharacteristics in the pathogenesis and further treatment opportunities are also covered. Moreover, drug repurposing efforts to identify the novel therapeutic effects/uses of the existing drugs are also discussed. During these studies, it was found that few drugs used for cardiovascular diseases and malaria (FDA approved: Verapamil, Nimodipine and Diltiazem and Chloroquine) have also exhibited potential against Ebola virus infection. Moreover, natural product obtained from Chinese and Japanese herbs (Tetrandrine), have inhibitory effect against Ebola virus. These finding can also be exploited for further drug discovery research.

Keywords: Ebola virus lifecycle, Transmission, Sign and symptoms, Proteins function, Treatment.

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Introduction

Ebola virus disease (EVD) sporadic and deadly disease caused by Ebola virus. There are five virus strain has been found according to different location of world in different pathophysiological conditions. Ebola hemorrhagic fever is another name of the EVD. According to the World Health Organization (WHO), there is up to 90% fatality rate in occurrence of EVD. It was first identified in Democratic Republic of the Congo and Sudan in 1976. Since then, there have been intermittentepidemics in Africa. In 1989, the Reston Ebola virus was first discovered (in USA). The monkeys originated from Philippines (crab-eating macaque), were infected from virus and died. In 2009, Reston Ebola virus antibodies were found in the six people infected from pigs in the Philippines with no symptoms. This virus is not highly pathogenic for human as compared to other Ebola viruses.However, WHO has been public health alert to the Asia-Pacific region about the newly emerging disease in animals and humans.

WHO reported that total number of 5,459 deaths were reported in six affected countries (the United States of America Guinea, Spain, Sierra Leone, Mali, andLiberia) and twopreviously reported countries (Senegaland Nigeria) [WHO report on Ebola response roadmap Situation: 1 October 2014] [1-4]. According toCenters for Diseases Control and Prevention (CDC) (USA), Ebola virus infections (28,639 new cases) and deaths (11,316 cases) were reportedin March 2016. All over the world, Ebola virus is mostly found in remote village in Central and West Africa [2, 3, 4].

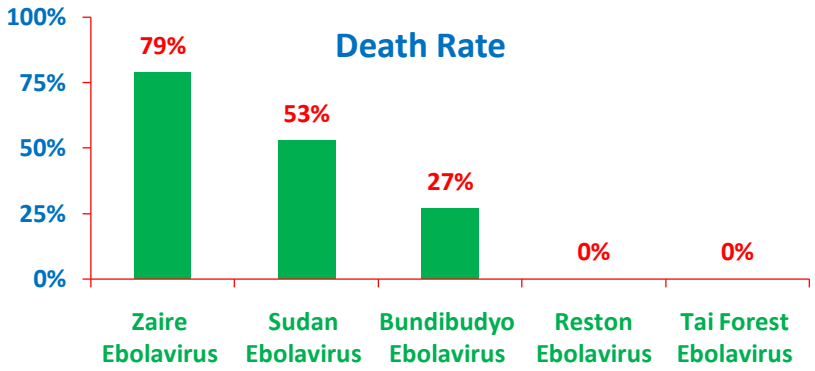

Fig1: Death rates of the 5 Ebola virus species [1-7]

Etiology and Transmission

Ebola is zoonotic virus (spread to the humans from non-human animals). The natural host of this virus is Fruit bats. There are five types of Ebola virus have been foun din different geographical location (See below Table 1).

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Table 1: Ebola virus belongs to the Filoviridae family. It comprises five distinct species [4-5]

Name of Ebola Virus	Geographical location
Bundibudyo Ebolavirus (BDBV)	Uganda
Zaire Ebolavirus (EBOV)	Congo and Gabonese Republic
Sudan Ebolavirus (SUDV)	Sudan and Uganda
Reston Ebolavirus (RESTV)	Philippines
Tai Forest Virus (TAFV)	Republic ofCôte d'Ivoire/Ivory Coast

In chimpanzees and gorillas, EBOV and TAFV species were observed in 1994. It has been found that person who handing these infected animals (Gorillas,Monkeys,Porcupines,Chimpanzees,Fruit bats,Forest antelope) were ill or dead in Africa[4, 5].Handling of these animal people can get infected with Ebola virus (documented by WHO).

Transmission from animals to humans

If human is having the close contact with body secretion of infected animals (organ or body fluid and blood secretion), then infection is transmitted to the human. Here is the main cause of the transmission [6-8].

- **Blood-**Eating infected/Slaughtering animals
- **Waste products-**In African caves and underground mine workers (close contact with the urine or feces of infected bats). [7,8]

Transmission from human to human

The human to human transmission is possible through direct contact. It may easily transfer to thousands of people. This endemic very difficult to control. It can be occurred by several ways, including[6-9]:

- Direct contact (Mucus membrane, body secretions/fluids, and broken skin)
- Indirect contact (from the environment if it is contaminated with virus)
- Semen of the infected people and people or who just recovered from EVD

This disease does not contagious until symptoms present in the infected person. Most importantly family members are always on the high risk if one member got infected with the Ebola virus. Medical practitioner or doctor may get infected if they do not use protective care (as per WHO). Every medical or surgical equipment's need to be sterilized properly before again use to other patients [6-7].

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Signs and Symptoms

EVDcharacterized by abrupt high fever (not present in generally) is a severe acute viral infection withthe symptoms like: intense headache,sore throat, severe weakness and muscle ache. After some time, this infection is appeared to have other symptoms likerash, vomiting, impaired kidney,diarrhea, and liver function (high level of liver enzymes). In some cases, bleeding may also present in inside and outside the body (according to WHO). According to WHO, symptoms is appeared after 2-21 days of infection. Person is having the virus in semen of the infected man after the 61 days of onset of disease. Now person can able to transmit the disease to other human. The symptoms are extremely nonspecific in the beginning- Ebola looks like almost anything (similar to other disease)[4, 6-9].

According to the CDC, the patient may also have the following symptoms [WHO report, 2015]: Meningitis, Typhoidfever, Malaria, Hepatitis, Shigellosis, Cholera, Relapsing fever, Leptospirosis, Plague, Rickettsiosis, Abdominal pain and Other viral hemorrhagic fevers.At the late stage of disease, bleeding from mouth and nose, this called hemorrhagic syndrome. Typically, this is present in 30 to 50% of patients.

Series of common diagnostic tests are used for diagnosis of EVD as per follow (from WHO Report)[4, 6, 8-10]:

- Serum neutralization test
- RT-PCR (Reverse transcriptase- polymerase chain reaction) assay
- Cell culture for virus isolation
- Antigen-capture detection tests
- Antibody-capture ELISA (enzyme-linked immunosorbent assay)

Life cycle of Ebola virus

Ebola Virus Genome and its proteins

- The EBOV belongs to Filoviridae family and having RNA virus. The 19-kb linearssRNA which is non-segmented. This genome encodes different structural and non-structural proteins.These are nucleoprotein (NP), virion protein 35 (VP35), VP30, 3′ non-coding region (leader), VP40, glycoproteins (likesGP, ssGP, GP1,2), VP24, 5′ non-coding region and RNA dependent RNA-polymerase[11].

Functions of different proteins in Ebola life cycle:

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- GP protein is responsible for important functions in extracellular environment and the virion proteins (VP40, VP35 and VP24)are having intracellular roles (Details is given in **Table 2**).
- The GP gene encode for three different products which consist of soluble GP (sGP) [lacks of transmembrane domain] and small soluble GP (ssGP), GP1 (receptor binding) and GP2 (viral fusion) subunits[12, 13].
- GP is located on the virion surface (only viral protein). This is exerting very important functions like attachment and fusionof the virion to the host [14-16].
- By GP1,2 is synthesized by transcriptional RNA editing. After the post-translation, it is cleaved into two disulphide subnits; one is surface unit which is called GP1 and other is membrane unit which is called GP2 [17-18].
- GP1 contains receptor binding site (RBS) to attach to host cell and a domain which defend the RBD from immune systems. For viral entry (into host), receptor binding and cellular tropism, RBS of GP1 is responsible for it [16, 17].
- GP2 helps in binding of membrane of host endosomal cell (acidic pH) to the viral membrane (through macropinocytosis). Acidic pH of the endosomes is responsible for cleavages of the GP1 [16-18].
- Acidic environment is present in endosomes. lt is important for activation of cysteine proteases:Cathepsin B and Cathepsin L. These proteases are responsible for the cleavage of EBOV.
- The fusion between endosomal and virusmembrane is done by GP1,2 [16-17].After of the virus entry, two receptors are found to important for fusion that are the Niemann-Pick C1 (NPC1) receptor and two-pore segment channel 2 (TPC2). At this time, the conformational changes occurred in the GP2. These areenabling the release of viral genome into the cytoplasm [16, 19-20].
- Host immune system is suppressedby VP35 and VP24 proteins.
- Using host system, Ebola virus is synthesizing the new virions via transcription and replication of RNA with help of VP35, VP30, and NP, L-protein.VP40 and VP24 is having role in replication and transcription regulation.However, VP30 is responsible for transcription initiation only. These available protein in Ebola virus can be used as an attractive target for drug design and discovery for new therapeutic intervention [16-20].
- For virus assembly and budding, matrix protein VP40 is very much important[16, 18, 20].

Table2: Functions of different Ebola proteins in its life cycle [21]

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Viral Protein	Main Functions	Other Functions
L	-Regulation transcription	-
VP40	-Viral budding and assembly	-HampersRNA interference
NP	-Protection of viral genome from degradation by encapsulation -Important part of RNA protein complex	-
VP30	-Initiates transcription	Impedes RNA interference
GP	-Fusion and entry of Ebola virusin host cell	-Reductionsof barrier in endothelial cells. -Responsible for destruction of T-lymphocytes -Producing cytotoxicity in cells in later stage
VP35	-Inhibits interferon signalling -Dendritic cell impairment in maturation -Impedes RNA interference -Blocking protein kinase R Inhibits antiviral effects by	-Responsible for formation of viral complex with VP30 and NP -Regulation of RNA synthesis mediated by NP-RNA interactions
VP24	-Inhibition ofinterferon signalling by interference of NF-κB and STAT signalling pathways	-Nucleocapsid assembly and stability -Regulation of central dogma process

Different treatment available for EVD

According to Food and Drug Administration (US-FDA), till date there is no drug is approved againstEbola virus. Most of the drugs are in clincal trial (soon may available for the treatment) (Source: https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/ebola-preparedness-and-response-updates-fda, accessed on date: 27-11-2019).But some guideline is given by WHO for incentive supportive care in Ebola virus infection, and often includes:

- Patient's fluids and electrolytes balancing
- Keepingthe blood pressure and oxygen status normal
- For any complicated infection, treatment has to take by a patient

Several vaccines are designed and tested [found satisfactory in animal model], but not available for clinical use [6, 7-9].Recently, a breakthrough for the treatment of Ebola virus was announced in August 2019 using monoclonal antibodies. The monoclonal antibodies (REGN-EB3 and mAb114) are found very good response in randomized controlled trial. It was found that the single dose REGN-EB3 intravenous treatment is decreased the mortality in the patients, especially in early stage strongly. On other hand mAb114 is having the similar effect as REGN-EB3. The US-FDA have been given orphan drug status (licensing not done)

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[11, 22].Both are being made available to all patients in the Congo. Moreover, first human clinical trials data are become available for the following three candidate vaccines (**See below Table**):

Name of the Vaccine	Developed by	Dose	References
rVSV-ZEBOV (V920)	Merck	Single dose	[23]
Ad26-ZEBOV/MVA-BN-Filo	Bavarian Nordic GmbH	Prime-boost regimen	[24]
ChAd3-EBO-Z	Bavarian Nordic GmbH	Tested in either a single dose (GlaxoSmithKline) or in combination with a booster dose of other vaccine (MVA-BN-Filo vaccine)	[25]

Some of the drugs and vaccines are also found in the literatures which is found promising effect in Ebola virus infection. However, lot of Ebola inhibitors (tested in vitro and in vivo studies) have also been listed in the literature(see **Table 3**) [26].

Table 3: Ebola therapeutics reported in different research studies [18]

Chemical Agent	Action	Company Status	US-FDA Status	References
T-705 (Favipiravir)	Broad-spectrum antiviral drug: against many RNA virus	Toyama Chemical of Japan	Not approved (found promising)	[27-29]
BCV, CMX001 (Brincidofovir)	Active against dsDNA viruses, however Ebola is dsRNA virus	Chimerix of Durham, NC,	Not approved (found promising)	[30-31]
BCX4430; Immucillin-A (Galidesivir)	Broad-spectrum antiviral effectiveness against a range of other RNA virus	BioCryst Pharmaceuticals	No plan for Ebola virus testing	[32]
JK-05	Inhibitor of the viral enzyme RNA polymerase	Sihuan Pharmaceutical	Not approved (Copy of Favipiravir)	[18]
TKM-Ebola	This is small interfering RNAs. It is targeting three proteins in Ebola virus life cylce: VP24, VP35, and Zaire Ebola L polymerase	Arbutus Biopharma (formerly Tekmira Pharmaceuticals Corp.)	Phase II trial failed, so changed to hepatitis B testing	[33]
ZMapp	Ebola glycoprotein epitopes	license by	Not approved yet	[34]

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(monoclonal antibodies)		Mapp Biopharma-ceutical	(in clinical trial)	
NSC62914	Scavenger of reactive oxygen species		Not approved (because of compound toxicity)	[35-36]
FGI-103	Replication inhibitor (not yet completely)	-	Not approved	[37]
FGI-104	Inhibiting the protein TSG101	-	Not approved	[38-39]
FGI-106	Not complete known, but speculated viral entry inhibitor active against positive or negative RNA virus	-	Not approved	[18, 26, 40]

Some of the drugs that emerged from already available marketed drug by drug repurposing approach. This means, drug is invented for one disease but also found new therapeutic use in other disease. Some of the drugs which identified through this approach are mentioned in the **Table4**.

Table4: Available drugs which are identified by repurposing process

Name of Drugs	Repurposed of the drug in Ebola infection	Parent function	Reference
Convalescent blood serum	• Neutralizing antibodies and T-cell responses - IgG level increased - VP40 and NP directly inhibited • Clearing the viral antigen from the circulation and cytotoxic T cells activation	Whole blood or plasma from a patient who has survived a previous infection, considered to be especially rich in antibodies against the infectious agent of the disease (WHO report)	[41-42]
Chloroquine	• Able to increase endosomal pH • As an entry inhibitor for many viruses • Targeting the Cathepsins L cleavage phenomena (A broad-spectrum)	Anti-malarial	[43]
Cationic amphiphiles	• Amiodarone: Potent entry	Used in	[44-49]

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(Dronedarone, Amiodarone,Verapamil, Clomiphene, and Toremifene)	inhibitor (Niemann-Pick type-C1 dependent). • Clomiphene, and Toremifene: Entry inhibitor (indirectly through NPC1) • Dronedarone: Similar to amiodarone activity • Verapamil: Similar to amiodarone activity	cardiovascular diseases	
Na+/K+ exchangers (amiloride and its derivatives)	Potent dose-dependent (at non-cytotoxic dose) as an entry inhibitor and inhibition of infection of the EBOV.	Diuretics (Potassium sparing) to treat hypertension and cardiovascular disease	[50]
Na+/K+-ATPase pump inhibitors (Cardiac glycosides)	• Ouabain: inhibitthe EBOV replication (in human MRC-5 cells at non-cytotoxic conc.). • Digoxin, and Digitoxin: Role is not clearly understood.	This are cardiac glycosides (used in cardiovascular disease)	[51-55]

Prevention and control

According WHO, these are the precautions that can be used to reduce the chance of infection and control [42].

Controlling in domestic animals

- Regularlywashingof the animal (Pig or monkey farms).
- Disinfection of animals with NaOCl (Sodium Hypochlorite) or other detergents.
- If virus infection is suspected, then immediately premises should be closed for no use further or quarantined.
- Close supervision of infected animal and its isolation from the non-infected animals.
- Isolate the infected animal from the other animal and make restricted movement of animals to other non-infected areas. This can reduce the spread of the disease.
- Safely incineration or burial of corpses (dead infected animals).
- Animal health surveillance system should be established and new case must be informed early to the human public healthand veterinaryauthorities[1, 4, 7, 8].

Reducing the risk of Ebola infection in people

- Gloves or other protective items must be used for handling of the infected Animals and people.
- Cook the food [Animal products (blood and meat)] thoroughly before take.

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- Regular cleaning of the hospitals and medical equipment's should be done from the disinfectants after visiting the infected person.
- Safely buried of the infected people [1, 5, 7-9].

Controlling infection in health-care settings

Health professionals should follow standard safeguards consistently with all patients – regardless of their diagnosisall the time during practices, including [4, 6-10]:

- Respiratory hygiene
- Safe burial practices
- Use of personal protective equipment (according to contact with infected materials)
- Safe injection practices
- Basic hand hygiene

Risk factors for Ebola

Person can be on high risk if:

- Traveling to areas of Africa (where infected people is living or confirmed case of Ebola is present).
- From Africa or the Philippines, importing animals for research work
- Involve in the medical care of the infected people and protection must be taken to care the infected people like sterilized syringes or cotton, use gloves and mask, etc.
- During cremation of dead body (infected people). [1, 4, 7-9, 11]

Conclusions

There is an alarm for EVD as it is contagious and very less opportunities for the treatment in the market. It is mainly found in West Africa, Sudan, Congo and. But it is sporadically found in other country due to tourist visited in the above-mentioned countries. The WHO gave few guidelines for prevention, control and treatment of the disease.But still a challenge for control of this disease as it is transmitted through the human to human interactions also. However, 90% transmission occursthrough the infected animals.

In the life cycle of Ebola virus lot of proteins [NP, VP35, VP30, VP40, VP24, glycoproteins (like sGP, ssGP, GP1,2) and RNA dependent RNA-polymerase]are present which are pivotal role in multiplication and survival of the virus in the human. Infected people get immunocompromised due to attack of the virus in the human immune system. These proteins can be used to design and discovery novel drugs.

As of now, there is no reported treatment for the virus.However, some of the drugs are being used for the treatment of the Ebola infection. It was reported that few marketed drugs (used in

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cardiovascular disease) can be used Ebola virus infections/diseases, like Verapamil, Nimodipine and Diltiazem. In addition, antimalarial drug (Chloroquine) is found to have effect in Ebola Disease. Moreover, Chinese and Japanese herbs Tetrandrine, have inhibitory action on Ebola virus. These drugs can be used further designing/identification of novel therapeutics. These finding suggested that Ebola is having different drug targets as also present in other virus, which can be further exploited to design and discovery novel drugs/leads with excellent potency and efficacy.

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