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Ebola virus disease: Current perception of clinical features, diagnosis, pathogenesis, and therapeutics

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Summary. – Zoonotic transmission of highly pathogenic viruses, are a cause of deadly epidemics around the globe. These are of particular concern as evident from the recent global pandemic due to Coronavirus disease 2019 (COVID-19). The genus *Ebolavirus* belongs to the *Filoviridae* family and its members are known to cause the Ebola virus disease (EVD), a highly contagious disease with a mortality rate of approximately 90%. The similarity of the clinical symptoms to those of various tropical ailments poses a high risk of misdiagnosis. Diagnostic strategies currently utilized include real time reverse transcriptase polymerase chain reaction, amongst others. No specific treatment exists at present, and the management of patients is aimed at the treatment of complications augmented with supportive clinical care. The recent outbreak of EVD in West Africa, which began in 2014, led to accelerated development of vaccines and treatment. In this review, we contemplate the origin of the ebolaviruses, discuss the clinical aspects and treatment of the disease, depict the current diagnostic strategies of the virus, as well discuss its pathogenesis.

Keywords: Ebolavirus; viral origin; treatment; pathogenicity of Ebola; Ebola virus disease

1. Introduction

Ebola virus disease (EVD) is caused by the ebolaviruses (EBOV), which belong to the *Filoviridae* family, and can be described as one of the deadliest epidemic viral diseases (Baseler *et al*., 2017). The average mortality rate due to EVD is up to 90% (Longet *et al*., 2021). The first case of EVD was reported in 1976 from the northern Democratic Republic of the Congo (DRC). Later, it was also reported in South Sudan with parallel outbreaks. As a result of activities with high risk of infection without the implementation of safety precautions, the disease spread and became an epidemic (Rajak *et al*., 2015; Breman *et al*., 2016). The viruses of concern were genetically related but belonged to discrete subtypes; *Zaire ebolavirus* (EBOV) and *Sudan ebolavirus* (SUDV), respectively, despite geographic and temporal coincidence. This was followed by an outbreak of viral hemorrhagic fever in May 1995, in Kitwit, Democratic Republic of Congo, as reported by the Centre of Disease Prevention and Control (CDC) (Khan *et al*., 1999). Diagnostic testing revealed the presence of EBOV infection (Khan *et al*., 1999). During the recent outbreak, dated from 2014 till 2016, 28652 cases were reported, of which 11325 people died, which is considered the largest outbreak till date (Bell *et al*., 2016; Baseler *et al*., 2017). The second largest outbreak, was reported by Democratic Republic of Congo Ministry of Health, in August, 2018. By November 17, 2019, a total of 3296 cases were reported. Out of these, 2196 EVD cases resulted in fatalities (Aruna *et al*., 2019). Furthermore, EBOV have the capability of

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Abbreviations: CDC = Centre of Disease Prevention and Control; BSL = biosafety level; CT = cycle threshold; EBOV = ebolaviruses; EVD = Ebola virus disease; ELISA = enzyme-linked immunosorbent assay; GP = glycoprotein; detection test; IgG = immunoglobulin G; IgM = immunoglobulin M; Mab = monoclonal antibodies; NP = nucleoprotein; RT-PCR = reverse transcription polymerase chain reaction; WHO = World Health Organization

person-to-person transmission, which explains their role in major epidemics (Khan *et al.*, 1999). The purpose of this review is to describe EBOV pathogenicity as well as detail the clinical aspects and manifestations. Moreover, transmission of the disease, diagnosis and treatment are also deliberated upon.

2. Origin and natural reservoir of EBOV

It is understood that the deadly West African EVD epidemic in 2014 stemmed from a transmission incident involving a 2-year-old boy in Meliandou, Guinea (Saéz *et al.*, 2015). The virus is believed to be of zoonotic origin and this was investigated via wildlife surveys, interviews, and molecular analyses of environmental and bat samples. No evidence for an epidemic was found in larger wild species, leaving the natural reservoir of EBOV unidentified (Marí Saéz *et al.*, 2015; Courtier *et al.*, 2020). Fruit bats, porcupine, rodents, dogs, an assortment of laboratory animals (inclusive of hamsters, guinea pig and mice) and non-human primates (baboon, macaque, chimpanzee, monkey and orangutan) could be affected by the virus. Further studies have revealed that arthropods do not act as EBOV vectors (Gumusova *et al.*, 2015). In addition to the above-mentioned EBOV reservoirs, animal carcasses are considered as a significant source of filoviruses in the wild. According to the Food and Agriculture Organization of the United Nations, the EBOV outbreak may be associated with infected apes that have been hunted and consumed as food. Chimpanzee, gorilla and duiker corpses may be the prime cause for the occurrence of human infection (Gumusova *et al.*, 2015). Research during the human outbreaks of EVD revealed that bats may have acted as common reservoir for the virus. In a recent study, it was found that the Egyptian fruit bat (*Rousettus aegyptiacus*) has immunoglobulin G (IgG) specific for EBOV in most of the animals captured in Gabon and Republic of Congo. Furthermore, 5% of the bats captured during the EVD outbreak in these 2 regions had EBOV-specific IgG, however, 1 year after the outbreak, the percentage of bats with EBOV-specific IgG dropped to only 1% (Pourrut *et al.*, 2007). This shows that *R. aegyptiacus* may indeed be a potential natural reservoir for EBOV, because the EBOV-specific IgG concentration in their serum increased and decreased. The index case is thought to have stemmed from a child playing in a hollow tree, which was housing a colony of insectivorous free-tailed bats (*Mops codylurus*), although the exposure to the fruit bat is common in the region. Bats of the species *Mops codylurus* are considered as a potential source of EVD outbreaks, and experimental data shows that this species is capable of surviving experimentally-induced infections. This reaffirms the significance of expanded sampling attempts for further understanding of the ecology of the EBOV (Marí Saéz *et al.*, 2014).

Further work was carried out in Africa where 4,022 bat blood samples were analyzed, and antibodies against EBOV were detected in a genus of insectivorous bats and a further six species of fruit bats (De Nys *et al.*, 2018). In a different study that was accomplished in Sierra Leone, the genome of a novel ebolavirus, namely the Bombali virus, was identified in free-tailed bats that were present in human dwellings, suggesting probable transmission to humans (Goldstein *et al.*, 2018).

Given that bats are thought to be the natural reservoir for many viruses such as Ebola, Marburg, Influenza A, Dengue, Lyssaviruses, and Coronaviruses, including the novel coronavirus causing the present pandemic (Bonilla-Aldana *et al.*, 2020), it is logical to investigate how these species are able to thrive, despite being infected with these viruses. Previous studies have suggested that animals that live in polluted environments, or those that are exposed to heavy metals, pollution, microbial infections or reside in conditions that would be detrimental to *Homo sapiens*, may have characteristics, which allow them to survive and even thrive in such conditions (Mandl *et al.*, 2018; Akbar *et al.*, 2019; Siddiqui *et al.*, 2020; Soopramanien *et al.*, 2020). This leads to the question how are bats themselves able to tolerate these viruses, while also possessing longevity in comparison with similar-sized land mammals? Studies reveal that bats have evolved multiple mechanisms to suppress inflammation, in particular by dampening nucleic acid sensing pathways (Gorbunova *et al.*, 2020). It will be interesting to study whether the gut microbiota of the bat contributes to its ability to fight pathogens, given the increasing number of recent studies that have shed light on the contribution of the gut microbiota to the host overall well-being (Heyde and Ruder., 2015; Siddiqui *et al.*, 2020). Moreover, the molecules or metabolites secreted by the gut microbiome of these species should be investigated for their anti-viral abilities.

3. Clinical aspects

The onset of EVD is characterized by a combination of generic symptoms including myalgia, asthenia, headaches, fever, dyspnea, delirium, vomiting, diarrhea, hiccups and conjunctivitis (Rajak *et al.*, 2015). The symptoms further include the onset of signs such as tiredness, fever, sore throat, headaches, weakness, muscular pain, skin rash, loss of appetite and cough in the prodromal phase of the disease. This is followed by fever, fatigue, abdominal pain, nausea, vomiting, secretory diarrhea, bruising and bleeding from gums, anxiety and petulance accompanied by fright, seizures, anxiety, hallucinations, irritability

Table 1. Detailed characteristics of Ebola virus disease

Phase of Ebola virus disease (EVD)	Duration	Clinical progression of disease	Symptoms	Symptomatic treatment	Clinical features	Preferability of the diagnostic tests	Treatment
Prodromic phase	1–3 days which are followed by an incubation period of about 5–9 days; ranging from 1–21 days	Non-specific febrile syndrome	Tiredness, sudden onset of fever, sore throat, headaches, weakness, muscular pain, skin rash, Appetite loss, cough	Acetaminophen (Paracetamol), Morphine, Fentanil (fentanyl)	Feverish (<38°C) or remittent fever, fatigue, myalgia	Antigen-capture ELISA, IgM ELISA, PCR including real-time quantitate (qPCR), Virus isolation	Antipyretics, oral hydration
Systematic involvement	3–10 days	The involvement of liver, gastrointestinal pathway, pancreas and kidneys	Consistent fever, fatigue, abdominal pain, nausea, vomiting, secretory diarrhea, bruising and bleeding from gums Anxiety and petulance	Acetaminophen (Paracetamol), Morphine, Fentanil (fentanyl), Imodium (Loperamide), Metaclopramie, Ondansetron; NG tube is also recommended (Nasogastric Intubation), Diazepam, Haloperidol, Chlorpromazine	pulse temperature dissociation as a result of high temperature (relative bradycardia), progressive lethargy, partial remission with intensive care inflammation of gums resulting in bleeding, liver enlargement, spleen enlargement, gross hematuria, proteinuria, lymphopenia, thrombocytopenia, abnormal renal and liver functional tests. Increment in Alanine transaminase (ALT) and aspartate aminotransferase (AST) while that in AST is more than the increase in ALT.	IgM and IgG antibodies	With the utilization of strict infection control measures the involvement of organ systems could be detected at an early stage, the utilization or personal protection equipment (PPE), supportive care measures should be adapted, Antipyretics, oral and aggressive intravenous hydration, antimalarials, antibiotics EBOV-specific therapy inclusive of Zmapp or REGN-1EB3 or mAb11
	–	The involvement of neurological system	Consistent high temperature including misunderstanding, fright, seizures, anxiety, hallucinations and irritability. The response to simple orders is reduced with the advancement of the disease.	Diazepam, Haloperidol, Chlorpromazine treated with NG tube	Deep prostration, alterations in mood, rare occurrence of seizures, coma, Complete dependence on caregivers in the community and critical/acute care measures in hospitals		Antipyretics, aggressive intravenous hydration, antimalarials, antibiotics with good central nervous system (CNS) absorption, EBOV-specific therapy: Zmapp or REGN-1EB3 or mAb11 plus remdesivir
Failure of organs	7–16 days (25%–90% mortality)	Systemic involvement	Nonresponsive and comatose, no response to simple orders. Bleeding from all mucous membranes and all orifices Hiccups (sign of terminal illness)	–	Hypovolemic, severe sepsis or septic shock, acute renal insufficiency	Retrospectively carried out in deceased patients; Immunohistochemistry analysis, PCR, Virus isolation	Intensive care with circulatory/ hemodynamic and ventilatory support, renal dialysis, transfusions EBOV-specific therapy: Zmapp or REGN-1EB3 or mAb11 plus remdesivir, Noninvasive or invasive mechanical ventilation in inclusion with the previous therapy
		Adult respiratory distress syndrome	Shortness and rapid breathing, chest pain, cough, resulting in bluish skin coloration		central and peripheral cyanosis, severe dyspnea at rest, jaundice, drowsiness		

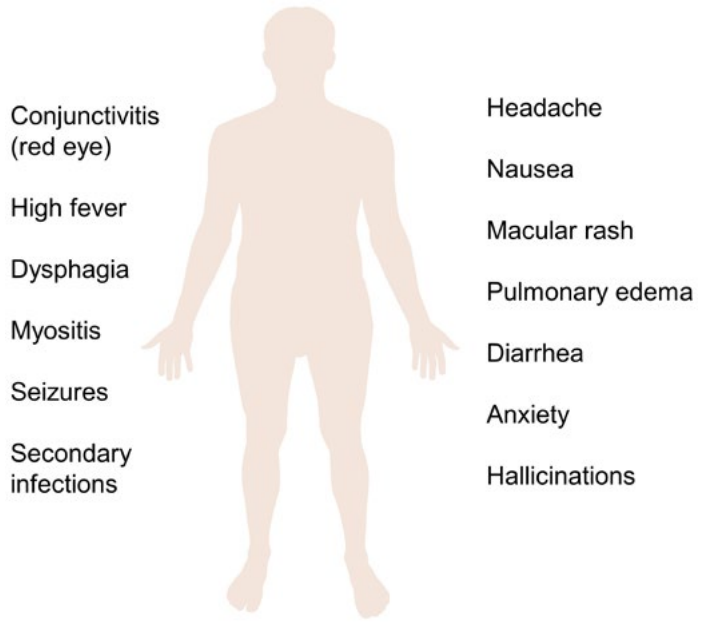

Fig. 1

Symptoms experienced by individuals infected with the ebolavirus disease

and reduced response to simple orders as the disease advances. Ultimately the patient falls into a comatose state with no response, bleeding from mucous membranes and orifices, finally leading to total organ failure (Khan *et al.*, 2017; Furuyama and Marzi, 2019; Jagga *et al.*, 2019; Nicastri *et al.*, 2019). The progress of the disease leads to secondary infections, persistent neurocognitive abnormalities, gastrointestinal hemorrhage, meningoencephalitis, shock and hypotension as per the late complications (≥10 days) (Kaushik *et al.*, 2016). Thus, diagnosis requires knowledge of detailed history of the patient, in addition to full examination. The travel history of the patient or the burial of someone carrying the virus can also be noteworthy. In the early stages of the disease, acute febrile illness is the general manifestation (Rajak *et al.*, 2015).

Rapid and reliable diagnosis plays a crucial role in developing apt and applicable patient management, intensification of the healthcare resources utilization, and hospital or health center infection prevention and regulation (Martinez *et al.*, 2015). In such scenarios, collection of data from patients could serve as a base for the development of clinical diagnostic measures. Nonetheless, common language barriers inclusive of the patients' perilous state could question the reliability of such methodologies (Cournac *et al.*, 2016). When searching through the latest description of the 2014 to 2016 outbreak, a lack of the objective significant signs data, such as heart rate, respiratory rate and blood pressure was observed (Bah *et al.*, 2015). A clinically suspected case of EBOV requires laboratory confirmation for a reliable diagnosis. However, the level of EBOV in the organism is sufficient for laboratory detection not sooner than after 3 days following initial symptoms (Ghazanfar *et al.*, 2015). The seroconversion of EBOV is detected in blood after high levels of the circulating virus appear (Na *et al.*, 2014). Thus, a potentially hazardous situation for health care workers persists due to the delay in diagnosis of the disease (Salvaggio and Baddley, 2014). Detailed clinical characteristics of EBOV are summarized in Table 1 and the symptoms experienced by individuals suffering from EBOV are depicted in Fig. 1. Furthermore, it has been reported that the virus is may persist longer than previously thought by clinicians and scientists. Patients, who have survived the virus infection have reported several symptoms after a six month follow up period; including fatigue, anorexia and abdominal pain (Singh *et al.*, 2017). Recently, the antibody responses in healthy survivors of the virus were described (Adaken *et al.*, 2021). The stimulation model suggested that EBOV antibody reactivity declined over 0.5–2 years following recovery and follow-up of survivors with vaccine immunization should be considered in order to prevent reseeding an outbreak (Adaken *et al.*, 2021).

4. Diagnosis of *Ebolavirus*

Since 1976, several outbreaks of Ebola have occurred (Mattia *et al.*, 2016; Racsa *et al.*, 2016). Although there have

been advances in therapeutic and diagnostic methods for EBOV, and this has improved the prognosis to some degree, there are still limitations. With earlier detection of the disease, the prognosis could be improved further, in order to save lives (Okware *et al.*, 2015). The quest for accurate and responsive laboratory tests to detect EBOV and diagnose EVD as early as possible is ongoing (Ayukekbong, 2016; Uyeki *et al.*, 2016). During the Zaire epidemic, Dr. Ngoy Mushola reported in his clinical log the first clinical definition of EVD: "The illness is characterized by a high temperature of about 39°C, hematemesis, diarrhea with blood, retrosternal abdominal pain, prostration with 'heavy' articulations, and rapid evolution of death after a mean of three days" (Olupot, 2015). The World Health Organization (WHO)/CDC currently states that "any illness with onset of fever and no response to treatment for the usual causes of fever in the area, along with at least one of the following signs: bloody diarrhea, bleeding from gums, bleeding into skin (purpura), and bleeding into the eyes and urine", is a suspected case of Ebola.

However, diagnosis of EVD is problematic due to the similarity of signs and symptoms with those of various other tropical ailments such as typhoid fever, dengue or other viral infections (Martinez *et al.*, 2015) that can result in misdiagnosis (Kaushik *et al.*, 2016). In addition, establishing safe as well as practical diagnostic strategies for the high biosafety level EBOV in resource-poor environments is extremely difficult (Broadhurst *et al.*, 2016). Thus, a number of laboratory diagnostic techniques are considered for the detection of EBOV, and several novel diagnostic techniques are being developed and in the pipeline.

4.1 Cell culture

Cell culture of the EBOV is the conventional prevailing methodology to verify the presence of EBOV (Mérens *et al.*, 2017; Rojas *et al.*, 2019). The virus is usually cultured in Vero E6 African Green monkey kidney cells. Visualization of the isolated virus is carried out under an electron microscope or under an immunofluorescence microscope within five days of inoculation of virus (Broadhurst *et al.*, 2016). Nonetheless, detection of the EBOV requires biosafety level 4 (BSL-4) containment. In addition, these methods are constrained to research and public health laboratories, which require extensive infrastructure and setup (Feldmann *et al.*, 2013, Andreas *et al.*, 2015).

4. 2 Antibody detection

The detection of specific antiviral antibodies through serological assays in the serum of patients has been utilized for the demonstration of current or previous occurrence of infection by ebolavirus. In 1977, an indirect fluorescent antibody detection test (IFAT), which was based on the viral antigen-specificity of antibodies in convalescent-phase serum, would distinguish between the newly found ebolavirus from the closely related Marburg virus in the individuals who had recovered from the infection caused by these pathogens. To perform the procedure, the cell cultures were infected by the EBOV (or by the virus suspension from these cultures). These infected cultures were inactivated by irradiation, fixed onto the slide and incubated with sera from potentially exposed individuals. Bound antibodies were identified through a fluorescently labelled secondary antibody and immunofluorescence microscopy (Johnson *et al.*, 1977). IFAT played a significant role in clinical diagnosis during the first several outbreaks of EVD, however, it was considered to have suboptimal sensitivity and specificity. In addition, the need for BSL-4 biocontainment makes this method unsuitable for application in large scale diagnostics (Broadhurst *et al.*, 2016).

4.3 Enzyme-linked immunosorbent assay (ELISA)

ELISA is an early diagnostic tool, which has been frequently used to diagnose EVD (Coarsey *et al.*, 2017; Atre *et al.*, 2019; Jagga *et al.*, 2019). With its potential for swift and primary diagnostic development, it was utilised for the antigen detection of EBOV (Coarsey *et al.*, 2017) and was the most vital standard in the detection of the EBOV before the year 2000 (Ksiazek *et al.*, 1999). Of note, ELISA shows a high level of sensitivity (93%) in the acute phase of EVD. As the disease advances, in 1–2 weeks after the onset of symptoms, the level of EBOV antigens declines, thus decreasing the antigen detection sensitivity (Leroy *et al.*, 2000).

To overcome the flaws of antigen detection, a nucleoprotein- (NP) and glycoprotein- (GP) based methodology for the detection of the EBOV infection in humans was proposed in 1998 (Prehaud *et al.*, 1998). This NP- and GP-based ELISA method can be used to detect immunoglobulin G (IgG) or immunoglobulin M (IgM) (Kaushik *et al.*, 2016; Rojas *et al.*, 2019). When a pathogen or vaccine is introduced into the body of the host, the adaptive immune response is generated. As a result of this adaptive immune response, IgM antibodies are induced followed by the induction of IgG antibodies (Atre *et al.*, 2019). IgG antibodies are retained for several years, but a considerable number of EVD patients die even before the IgG antibody response is developed (Martinez *et al.*, 2015). Therefore, and relying upon the order of induction, detection of IgM through ELISA was preferred over that of IgG antibodies. The test for the detection of IgM antibodies is performed in the first week after the onset of suspected EVD symptoms,

however the peak of IgM antibodies is reached during the second week of ailment (Martinez *et al.*, 2015).

In 2001, a type of ELISA based on EBOV antigen-detection using the monoclonal antibodies (MAb) acquired by the immunization with NP (Zaire subtype), named as sandwich ELISA (or antigen-capture assay) was established (Niikura *et al.*, 2001). Detection of 30 ng of recombinant NP was achieved by this procedure. The corresponding region of NP stemming from the Reston and Sudan subtypes reacted with the utilized MAb. The system was capable of detection of very low levels of EBOV (Niikura *et al.*, 2001). Nonetheless, these applications still require BSL-4 facilities to perform EBOV detection and diagnostics, which limits their use in the local outbreak setting.

4. 4 Real-time reverse transcription polymerase chain reaction

At present, real-time reverse transcription polymerase chain reaction (RT-PCR) is a reliable diagnostic tool used for detection of EBOV infection. This tool offers better sensitivity and provides faster results, in approximately 2 - 3 hours, compared to other methods mentioned previously (Broadhurst *et al.*, 2016). Real-time RT-PCR uses reverse transcriptase enzymes to transcribe the EBOV viral RNA into cDNA, followed by the real-time PCR to amplify the cDNA. To allow the detection of the amplified cDNA, fluorogenic probes are incorporated that can bind to the double stranded DNA produced during the PCR process and emit a detectable fluorescent signal, thus, allowing the detection and display of the cDNA copy number (cDNA copy number can then be used to calculate the viral RNA starting quantity based on the standard curve). When running the real-time RT-PCR, the parameter that requires the most attention is the cycle threshold (CT), which indicates whether the fluorescent signal emitted by the fluorescent probe is able to reach the threshold value. If a lower CT is achieved it means that the sample has high EBOV-RNA initiation quantity. This also indicates that the patient has acquired EBOV infection.

Since real-time RT-PCR gives reliable results, it has been used in recent EVD outbreaks to diagnose patients for EBOV such as the recent EVD outbreak in West Africa from 2014–2016 (Crowe *et al.*, 2016). In a study conducted by Crowe and his colleagues (2016), which evaluated the information for 216 of 227 patients in the Bo District during a 4-month period. Outcome (death or recovery) was confirmed for 216 patients, but no information was available for 11 patients. Of the 216 patients, 164 were admitted but 52 died in the community before being detected. Of the 164 patients, 6 died before blood could be collected for confirmatory testing. In some cases, Ct values were missing and in others admission dates were missing. It was found that only 52 EBOV-infected patients out of the group of 60 patients survived the EBOV infection. This group of individuals had a CT value of higher than 24 (they had lower copy number of EBOV RNA). On the other hand, in the other group of 91 patients, in the same study, the CT value was lower than 24, and only 20 survived the infection (they had high copy number of EBOV RNA) (Crowe *et al.*, 2016). The results showed that those with low copy number of EBOV RNA (CT value of higher than 24) had a better chance of survival than those with higher amount of EBOV in them. Based on the research mentioned above, the efficacy and the sensitivity of real-time RT-PCR is evident and thus it has become the standard for EVD diagnosis. Several standard (nonautomated) real-time RT-PCR tests are approved by the FDA and the WHO, and are available as kits, commercially.

Nonetheless, establishing rapid and safe diagnostic strategies for the EBOV, a high-biosafety-level pathogen, remains particularly challenging, given the lack of resources available at outbreak settings. Diagnosis using RT-PCR in the outbreak setting requires field laboratories with corresponding infrastructure, comprising laboratory equipment as well as molecular expertise. Furthermore, collecting and transporting clinical samples safely is of utmost concern. Thus, it is necessary to work at the international level as well as locally, in the regions, where the virus is endemic, to foster much needed and innovative diagnostic tools as well as analysis of samples, incorporating appropriate biosafety processes (Broadhurst *et al.*, 2016). There are diagnostic tools in the pipeline comprising of nanotechnology-based tools, microchips, biosensors, lateral flow assays and next generation sequencing technologies (Singh *et al.*, 2017).

5. Pathogenesis

The EBOV is characterized by a single-stranded, nonsegmented, negative-sense RNA genome. The size of the genome is about 19 kb (Furuyama and Marzi, 2019). The single filamentous particle has a negative single-stranded RNA genome including seven transcriptional units. The transcriptional units code for seven distinct genes (Kaushik *et al.*, 2016). Nine proteins are expressed from these seven distinct genes (Simmons *et al.*, 2002; Kaushik *et al.*, 2016). Short extragenic regions called the leader and trailer sequences at present at the genome ends. These sequences consist of encapsidation signals in addition to replication and transcription promoters (Rivera and Messaoudi, 2016). Genes are flanked at the 3' and 5' by untranslated regions (UTRs). The ends are restricted by conserved transcriptional signals. These signals start close to the 3' end of the genomic sequence consisting of

a starting site and ending with a stop site, with intergenic regions separating the genes.

The genes are sequentially arranged as the 3' leader – nucleoprotein (NP) – virion protein (VP) 35, the matrix protein VP40, the glycoprotein (GP), the VP30, the VP24 and the RNA dependent RNA polymerase (L) – 5' trailer (Rojas *et al.*, 2019). Most of the genes encode a single protein product including nucleoprotein (NP); encoding the structural protein, glycoprotein (GP); encoding envelope glycoprotein, minor matrix protein (VP24) and matrix protein (VP40); as matrix proteins, polymerase cofactor (VP35), transcription activator (VP30) and RNA-dependent RNA polymerase (L); acting as the major non-structural proteins (Kaushik *et al.*, 2016; Rojas *et al.*, 2020). The GP gene exceptionally codes for three proteins and is essential for viral pathogenesis. The primary product of the glycoprotein (GP) gene is the soluble GP. However, via RNA editing mechanism, a full-length transmembrane structural GP protein is synthesized. Through further editing process, a smaller soluble GP will be produced, which is hypothesized to act as a decoy protein to bind to the anti-GP antibody secreted by the host immune system (Kaushik *et al.*, 2016; Rojas *et al.*, 2020). Differing functions are performed by each of the proteins; GP, VP40 and VP24 (membrane proteins) are required for the development of the filamentous virions, whereas NP, VP35, VP30, and L (i.e., ribonucleoprotein-RNP complex) play crucial roles in the processes of viral replication and transcription (Rojas *et al.*, 2020).

The transmission of EBOVs occurs via the contact of infected body fluids with skin lesions, mucous membranes or by nonintact skin, which allows the entry of the virus into the body, resulting in direct contact with target cells. Endothelial cells, monocyte/macrophage lineage, adrenal cells, immature dendritic cells and the Kupffer cells in the liver are usually infected by the EBOVs as demonstrated by in vivo studies in non-human primate models (Alvarez *et al.*, 2002; Hensely *et al.*, 2011; Baseler *et al.*, 2017). The diversification of target cells is primarily due to the capability of GP1 of EBOV to interact with an assortment of host-cell proteins (Rojas *et al.*, 2020).

One of the most vital receptors, inclusive in the attachment of the virus and its entry, are the lectins. These are present within the host membrane such as C-type lectins; dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin and its receptor (on dendritic cells, endothelial cells and macrophages) and human macrophage lectin specific for galactose/N-acetyl galactosamine on macrophages. Lectins assist in the form of co-receptors for the entry of EBOVs into dendritic cells (Matsuno *et al.*, 2016). Other receptors and coreceptors involve the asialoglycoprotein receptor present on the hepatocytes, the folate receptor α on epithelial cells (Chan *et al.*, 2001; Knipe and Howley, 2013), β1-Integrin, glycosaminoglycans, Tyro3, T-cell immunoglobulin, Axl, mucin 1 (TIM-1) and Mer (TAM) receptor tyrosine kinases. These receptors and coreceptors, because of their particular ability to interact with the GP1 viral protein, have been suggested as the EBOVs entry factors, which would explain the existence of diverse permissive cells (Rojas *et al.*, 2019).

It has been shown that the 'macrophage galactose-type calcium-lectin' contributes potentially to the relative infectivity of the viral GP (Fujihira *et al.*, 2018). NPC1, an endosomal protein, is an additional entry receptor. Recently, it has been reported to bind EBOV GP via domain C. This results in conformational variations in GP, which activates the fusion of membrane (Wang *et al.*, 2016).

Binding of GP to its receptor enables virion entry into the target cell by endocytosis (Rivera and Messaoudi *et al.*, 2016). The phosphatidylserine present on the surface of virions, in the case of EBOVs, interacts with the host cell membrane and results in the reorganization of the cytoskeleton. The internalization of the virion results in the formation of early endosome. Consequently, EBOVs are exposed to more acidic environment as trafficked to late endosomes. The low pH allows GP processing, subsequently assisting virion and host-cell membrane fusion (Chandran *et al.*, 2005).

In summary, a comprehension of the mechanisms of the EBOV-induced effects, would aid the development antiviral therapy and a vaccine. Of note, the EBOV doesn't display a great degree of variability, as many other viruses may do, to escape host immunity. However, the EBOV GP is able to alter function of the target cell.

6. Treatment of EBOV

Currently, no specific or approved antiviral treatment for EVD exists, and the treatment of patients is aimed at the treatment of complications supplemented by supportive clinical care (Nicastri *et al.*, 2019). Nonetheless, there are windows of opportunity for prophylactic treatment of EVD. Prophylaxis could be done at various levels, starting from pre-exposure prophylaxis, which involves non-pharmacological methodologies aimed at creating barriers and precautions before the spread of the disease. These applications are basically categorized under the scope of disease prevention. Management of EVD is problematic in urban and rural surroundings, thus firm and early implementation of infection prevention and control measures are required (Nicastri *et al.*, 2019). Moreover, teams of multidisciplinary trained personnel, biocontainment units, as well as engagement with the community and leaders are needed. Working with patients with EVD requires extensive training in infection control and pre-

vention measures, and health care workers often have to work in difficult conditions comprising extreme heat and/ or humidity while wearing personal protective equipment (Nicastri *et al.*, 2019). Other disease prevention measures recommended by the WHO include avoiding contact with animals in order to avoid exposure to the virus as well as isolation/ quarantine, limited handling of human remains, and managing exposure to the virus from human bodily fluids (WHO, 2014). Vaccination is a preventative strategy and is discussed in the next section. In the absence of preventive strategies or vaccines, the presence of antiviral compounds provides an opportunity to focus on post-exposure prophylaxis treatment that helps in the reduction of the severity of disease, transmission of the virus and clinical manifestation duration. Table 2 depicts a summary of therapeutic strategies against EVD.

6.1 Targeted therapies

A nucleoside analogue known as Favipiravir, results in the prevention of viral replication in the cell and, consequently, in the inhibition of infection (Kilgore *et al.*, 2015; Zhang *et al.*, 2017). The compound Favipiravir is an anti-viral agent that selectively and potently inhibits the RNA-dependent RNA polymerase of RNA viruses and has shown a reduction in the mortality rate of EBOV-infected mice (Bixler *et al.*, 2018). However, efficacy conclusion could not be drawn when this compound was utilized in a single-arm clinical trial (Jacob *et al.*, 2020).

The administration of convalescent plasma to individuals and small cohorts of EVD patients have been carried out for decades. A recent study conducted in Guinea in 2015 revealed that no difference was observed in the mortality rate of the 84 EVD patients, who were provided with two doses (200 and 250 ml) of the ABO-matched convalescent plasma, in comparison with the 418 untreated patients (Van Griensven *et al.*, 2016).

A combination of three monoclonal antibodies, ZMapp, prevented death of EBOV-infected macaques following the onset of viremia and fever. The uncontrolled clinical reports of possible ZMapp efficiency have provided hope but it is not clear if it will have a sufficient efficacy, because the ongoing studies have a limited number of patients, some of whom are in late stages of the disease (Qiu *et al.*, 2014).

A number of other antiviral compounds showed therapeutic promise when tested *in vitro* and also in animal studies. During the West African epidemic, many of these antiviral compounds were tested on patients with EVD as part of the clinical trial evaluation (Baseler *et al.*, 2017). Some compounds for the treatment of EVD have been evaluated in preclinical studies but have not been studied for the aspects of usage safety and their efficacy in humans. For instance, compounds, which interfere with the synthesis of the viral messenger RNA (TKM-Ebola) and the antisense oligonucleotides, or the compounds, which cause the inhibition of viral RNA polymerase function (inclusive of BCX4430 and GS-5734), show reduction in EBOV mortality in animal models. But such compounds have not been evaluated in controlled clinical studies. Moreover, therapy that targets disordered coagulation by the application of recombinant nematode anticoagulant protein C2 or the recombinant activated protein C has also shown improvement in the survival of macaques. But these potential therapies have also not advanced to a stage where they can be applied on human beings during trials (Baseler *et al.*, 2017).

6.2. Concentration and dosage of drugs

The lack of availability of approved drugs was particularly evident during the EBOV outbreak in the years 2014-2016 in West Africa. The outbreak proved to be an opportunity for the scientists to better understand the disease and eliminate it for good. Using several clinical trial designs, several therapeutic options were tested later in the epidemic. The applications involved ZMapp monoclonal antibody cocktail, various small molecules and rVSV-ZEBOV; a vesicular stomatitis virus-based candidate vaccine (Dyall *et al.*, 2018). A recombinant, replication-competent candidate vaccine, rVSV-ZEBOV, expresses a surface glycoprotein of Zaire ebolavirus. This vaccine proved quite efficacious in the prevention of the EVD. A single intramuscular dose of rVSV-ZEBOV (2×10^7 plaque-forming units applied into the deltoid muscle) proved effective in the prevention of the EVD. For the prevention of post-vaccination fevers, the patients were provided with ibuprofen or acetaminophen (Henao-Restrepo *et al.*, 2016). In spite of these advances, there is a dire need for the development of small-molecular therapeuticals, which can help in rapid responses to the EBOV. A rescreen of candidate drugs against the EBOV was carried out in order to identify the pairs, which block the virus synergistically in cell cultures. Some highly synergistic pairs include: sertraline/toremifene at a concentration of 12.5 μM and 25 μM, piperacetazine/aripiprazole at a concentration of 12.5 μM and 10 μM and amodiaquine/clomiphene citrate at a concentration of 10 μM and 2.5 μM, respectively. These pairs of approved drugs acted synergistically in blocking the EOBV infection in cell cultures (Dyall *et al.*, 2018). To test Favipiravir tolerance and its efficacy against EVD, the JIKI clinical trial was conducted in Guinea in 2014–2015. A dosing regimen of 1200 mg every twelve hours was anticipated for the maintenance dose. The dosing regimen was in compliance with a loading dose of 6000 mg (2400, 2400, 1200, 1200 mg) on the first day of the trial,

Table 2. Therapeutic strategies against Ebola virus disease

Treatment strategy	Description; mode of action	Intake strategy	Results; protection against virus	Usage by humans	Ebola virus disease (EVD) clinical phase	Drug company
Convalescence plasma (also called convalescence sera)	ABO-compatible convalescent whole blood, sera or plasma acquired from the EBOV survivors	Intravenous injection	The amount of Ebola NtAb titer increases in the blood of survivors in comparison with the deceased patients. The increased levels of anti-EBOV antibodies prove efficient in the control of the viral load. The EBOV-Makona infected rhesus monkey when treated with heterologous convalescent plasma did not depict 100% protection activity after the onset of the viremia. The trials conducted in Guinea and West Africa depicted no improvement in the survival of the patients. But some studies state that with the respective treatment strategy, only 1 out of 8 patients was deceased	Been subjected to usage since the EVD outbreak in KiKwit but no efficacy was determined till the clinical trials conducted in 2016	Phase III	N/A
ZMapp	A cocktail of triple human/mouse chimeric neutralizing antibodies which are inclusive of c13C6, c2G4, and c4G7, targeting the viral glycoprotein (GP). ZMapp is synthesized on the cellular lines of genetically modified tobacco plant (Nicotiana benthamiana)	Intravenous injection	The conductance of a controlled randomized trial in the West African patients depicted the efficacy of ZMapp but the statistical threshold of effectiveness of antibody cocktail was not up to the limits. The application of ZMapp depicted 100% reduction in the occurrence of the infection, on five-post challenge in NHP, in the rhesus macaques. In NHP, postexposure protection was observed till five days. Recovery was generated in inclusion with a decrement in the liver enzymes, petechia and mucosal hemorrhages. Protection was deliberated against systemic and airway-sustained EBOV infection, when ZMapp is subjected to mice via the aid of viral vectors. A reduction in the mobility of the virions which occurs in the mucus of the respiratory tract, in addition to the reduction of EBOV access to the respiratory epithelium.	Envisioned beneficial but no efficacy was determined in the PREVAIL trials	Currently in Phase I & II	Mapp Biopharmaceuticals (San Diego, USA)
REGN-EB3	A combination of human monoclonal specific anti-EBOV triple antibody assortment (inclusive of REGN3470-3471-3479), it could also be attained by the immunization of VelocImmune mice. The mixture targets the tri-non-overlapping epitopes present on EBOV	Intravenous injection	Safety, immunogenicity and pharmacokinetics of treatment were depicted in a phase I study in humans. High-levels of post exposure protection (by a single IV dose) in contradiction to EBOVs disease in NHP were demonstrated for up to 5 days	Anecdotal usage	Phase I-II	Regeneron
mAb114	A monoclonal antibody, identified after 11 years of infection, in a survivor of Kikwit outbreak (1995), DRC	Intravenous injection	The protection of macaques was carried out by the conduction of monotherapy accompanied with mAB114, from the fatal EBOV infection. In NHP, post exposure protection was retained by a single IV dose	Anecdotal usage is carried out. It is well-tolerated and safe in humans	Phase I	Ridgeback Biotherapeutics by US NIAID license
Remdesivir (GS-5734)	It is a prodrug of monophosphoramidate 1'-cyano-substituted adenosine nucleotide analogue, having antiviral activity in contradiction with the several variants of many filoviruses including EBOVs. It requires the host cell metabolism in order to pharmacologically active triphosphate (TP), inhibiting the EBOV RNA-dependent RNA polymerase which results in the inhibition of the viral replication	Intravenous injection	In EBOV infected rhesus monkey, the viral replication was reduced through the intravenous administration of Remdesivir, resulting in protection against the fatal disease. Key enzymes crucial for viral replication are disrupted in Sudan and Zaire species of EBOV. Through the subjection of ZMapp and Remdesivir a newborn acquiring congenital infection survived. In NHP, infected by EBOVs, Remdesivir results in the decrement in viremia and mortality. In NHP, post exposure protection was observed after the IV infusion till day 3-15	Anecdotal usage, usage in survivors depicting viral persistence in semen	Phase I & II	Gilead Sciences

Table 2. Continued

Treatment strategy	Description; mode of action	Intake strategy	Results; protection against virus	Usage by humans	Ebola virus disease (EVD) clinical phase	Drug company
Favipiravir (T-705)	6-Fluoro-3-hydroxy-2-pyranizecarboxamide, a licensed anti-influenza drug, which is also known as avigan. It depicts antiviral activity in contradiction to the RNA viruses. The viral replication is inhibited through the RNA Polymerase (L) enzyme (inhibitor). The antiviral activity could be shared against other RNA viruses such as Ebola	Oral	Survival chances were increased in the Guinea patients as depicted by a retrospective study. At the Sierra Leone-China Friendship Hospital, the treatment acquired a prolonged survival in addition to the load of virus in the patients. This efficacy of the drug was observed in the victims with low to moderate level of viral infection. In EBOV infected NHP, high doses resulted in prolonged survivals of the subject. 83% chances of the EBOV infection were reduced in the knockout mice for IFNR α/β/γ (IFNAGR KO) when treated with Favipiravir. A rapid elimination and decrease in the biochemical limitations of the severity of disease was also shown. Action against the Zaire EBOV and Marburg virus via the reduction in RNA levels was shown in mouse model.	Availability of stockpile. In low to moderate viremia, limited efficacy was represented. Well tolerated in humans.	Phase II & III, Approved for IAV JIKI, not yet tested on EVD patients	Toyama Chemical, Japan MediVector per Fujifilm

predicted to achieve stable concentrations after about 48 h. The highest maintenance dose attained was 800 mg twice a day with the continuation of the treatment for 5 days. The patients involved in the trial had a significantly lower mortality rate than those not included (Nguyen *et al.*, 2017).

7. Supportive care treatment

As indicated above, there is no specific treatment approved for EVD, thus the emphasis is on the supportive care. This includes intravenous fluid replacement with crystalloid fluids and vasopressors (Jacob *et al.*, 2020). Oral rehydration salts may be administered in the early stages of the infection, to replace fluid loss and at later stages of the disease, when symptoms like increased gastrointestinal fluid loss occurs, anti-emetic and anti-diarrheal agents can be utilised (Jacob *et al.*, 2020). Critically ill patients typically receive intravenous fluids, enteral nutrition, and electrolyte repletion. This is supplemented by monitoring of vital signs, infusions of vasopressors, and positive pressure oxygen therapy if required (Lamontagne *et al.*, 2018).

8. Developing a vaccine

After the onset of EVD epidemic in 2014, the high lethality of the disease prompted scientists to accelerate the development of appropriate vaccines against the virus in order to avoid future epidemics (Rojas *et al.*, 2019). The first one to be developed was the inactivated virus, which protected the guinea pigs from the EBOV infection. Since then the development of different forms of vaccines took place, which included DNA, virus-like particles (VLPs), recombinant viral vectors, recombinant proteins, replicative vector-based vaccines and non-replicative vector-based vaccines (Furuyama and Marzi, 2019; Rojas *et al.*, 2019).

The effectiveness of each of the vaccines has been tested upon and then evaluated in rodents or non-human primates. There are more than twelve vaccines currently in various clinical trial phases, each of which targets the EBOV GP but the elicited immune response varies (Marzi *et al.*, 2019).

By utilizing the plasmid, which encoded the sGP and GP, the first DNA vaccine against EBOV was developed. This vaccine provoked both the humoral and the T cell responses. The DNA vaccines are advantageous in comparison to the live attenuated vaccines, as they are safer to use and easy to produce. The DNA itself induces immune responses, and the protein synthesis of the host cell allows for the endogenous presentation of the desired antigen.

In 1998, the first effective immunization strategy via the utilization of a DNA vaccine against EBOV was described. After four doses of a DNA vaccine (encoding either EBOV GP or EBOV NP), 100% protection of the mice from the lethal EBOV challenge was shown. In non-human primates, DNA vaccination resulted in 83% protective efficacy with an optimized antigen expression (Grant-Klein *et al.*, 2015). With a combination of a DNA priming and an adenovirus boost (both of which encode EBOV GP), 100% protection efficacy was achieved. (Zhou and Sullivan, 2015).

The non-replicative vector-based vaccines involved the use of non-replicative vectors, which code for GP. High dosage of these vaccines is required to obtain a significant response and generate high tolerability. The attenuated Venezuelan equine encephalitis (VEE) virus acts as a candidate vector utilized in the preparation of candidate vaccines for EBOVs. EBOV GP or NP gene are introduced into the VEE RNA; the recombinant replicons are packaged into the VEE replicon particles (GP-VRP and NP-VRP). Vaccine trials have been carried out on BALB/c mice and guinea pigs. GP-VRP in combination with the NP-VRP or alone has proved to protect the guinea pigs and the BALB/c mice from the EBOV infection. But vaccination with just the NP-VRP only proved effective in mice. When C57BL/6 mice were immunized by the utilization of NP-VRP, almost 75–80% of the mice were protected against the lethal EBOVs. In addition to this, *Cynomolgus macaques*, when immunized with a dose of GP-VRP, were also completely protected against the lethal challenge of EBOVs (Rojas *et al.*, 2019).

An urgent meeting named "Ebola Vaccine - An International priority" organized by WHO, Geneva, was attended by public health organizations, scientists, pharma-industries and regulatory bodies. In the Ebola outbreak-2014, the potential of two vaccines was utilized. These were inclusive of cAd3, which was approved by GlaxoSmithKline and National Institute of Allergy and Infectious Diseases; and rCSVΔG-*Ebolavirus*-GP; which was approved by New Link Genetic and Public Health Agency of Canada. These vaccines were also discussed at WHO. The cAd3 vaccine showed immunogenicity and safety, but the production of a substantial amount of the vaccine is still a challenge. With the exception of the two mentioned drugs and a monovalent form of cAd3 vaccine, which was based on the Zaire strain and proved effective in Ebola outbreak in 2014 in West Africa, all other vaccines are merely in their preliminary stages. On the account of facing the challenge, WHO and other public health related agencies have asked pharma companies to enhance the production of vaccines in order to provide safety in advance and immediate therapy for, if any EVD epidemic occurs in the future (Kaushik *et al.*, 2016). At present, one vaccine, named "Ervebo", has been approved by the U.S. Food and Drug Administration for prevention against the EVD and other vaccines are in development with varying results (Piszczatoski and Gums, 2020). However, unanticipated manifestations of epidemics can make preventive vaccination of populations challenging (Martin *et al.*, 2020).

9. Conclusion

Ebolavirus disease, which is caused by the ebolavirus, poses a potential threat to human and animal health globally. This negative sense RNA enveloped virus encodes for 7 genes and consists of surface glycoprotein. These surface glycoproteins play a role in the attachment, fusion and the entry of the virus into the host cell and are a major component of immunogenicity. It is believed that in addition to many non-human primates, fruit bats and free-tailed bats may act as a reservoir for the virus, transmitting it to humans. The recent EVD outbreak clearly showed the lack of availability of a robust human health care system. This strongly suggests that there is a need to develop a resilient health care system that can be established even in poor resource settings. The treatment of EVD is a challenge, as there are no approved therapeutics yet. Although some diagnostic methodologies are generally used, which include ELISA and RT-PCR, novel diagnostic strategies need to be developed, which are rapid and of low cost. Recently, there has been an advance in the development of an Ebola vaccine, with some vaccine candidates that showed promise in clinical trials (Wang *et al.*, 2016). The most promising drugs tested yet include Favipiravir and ZMapp. The spread of the disease could be restricted to a large extent if precautionary measures are followed. The adaptation of public and personal hygiene is quite significant, as the resources and knowledge are not the only challenges when combating EBOV. Future studies need to be carried out to determine and define the doses and the duration of immunity elicited by vaccines. Furthermore, the use of vaccines against the EBOV is a vital strategy against this deadly virus.

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