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Ebola virus as a global health threat, a narrative review

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Abstract

The greatest Ebola virus disease (EVD) epidemic in recorded history is now occurring in West Africa. The Zaire Ebolavirus (EBOV), the virus responsible for this outbreak, is a member of the genus Ebolavirus, which combined with the genus Marburgvirus makes up the family of the Filoviridae. Among the viral hemorrhagic fevers, EBOV is one of the most aggressive viruses; case fatality rates of up to 90% have been documented. Multi-organ failure and serious bleeding problems are what cause death. The WHO recorded 5335 cases (confirmed, suspected, and probable) as of September 18th, 2014, with 2622 fatalities, yielding a case fatality rate of almost 50%. With a focus on pathophysiology, clinical symptoms, and therapeutic options, This review aims to provide an overview of EVD for clinicians.

Keywords: Ebola virus disease, pathogenesis, Diagnosis, treatment, filovirus

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Introduction

The Ebola virus is currently one of the most feared pathogens in the entire world due to its high pathogenicity for both humans and non-human primates. After being identified in 1976, the Ebola virus (EBOV) was largely forgotten until 1995, when it reemerged in Kiewit, Democratic Republic of the Congo (formerly Zaire)[1]. EVD outbreaks typically begin with a single case of possible zoonotic transmission, then spread from person to person through direct contact, contact with contaminated food, or contact with bodily fluids[2]. The symptoms of EVD include fever, gastrointestinal symptoms, and multiple organ dysfunction syndrome[3]. It has a high case-fatality rate. Twelve different filoviruses have been identified so far[4]. The seven filoviruses that have been identified in humans are either members of the genus *Marburgvirus* (Marburg virus (MARV) and Raven virus (RAVV) or the genus *Ebolavirus* (Bundibugyo virus (BDBV), EBOV, Reston virus (RESTV), Sudan virus (SUDV), and TaForest virus (TAFV) [5], as shown in Figure 1. Two major subtypes of filovirus disease (FVD) are recognized by the WHO International Classification of Diseases Revision 11 (ICD-11) of 2018: Ebola disease caused by BDBV, EBOV, SUDV, or TAFV, and Marburg disease caused by MARV or RAVV. EVD is a condition that can only be brought on by EBOV. This subcategorization of FVD is based in large part on mounting evidence of molecular distinctions between Marburg and ebolaviruses, distinctions that may affect the tropism of the virus-host reservoir, pathogenesis, and disease phenotype in unintentional primate hosts[5,6].

This review aims to provide an overview of EVD for clinicians, with the emphasis on clinical signs and symptoms, Diagnosis, pathogenesis, transmission and treatment options.

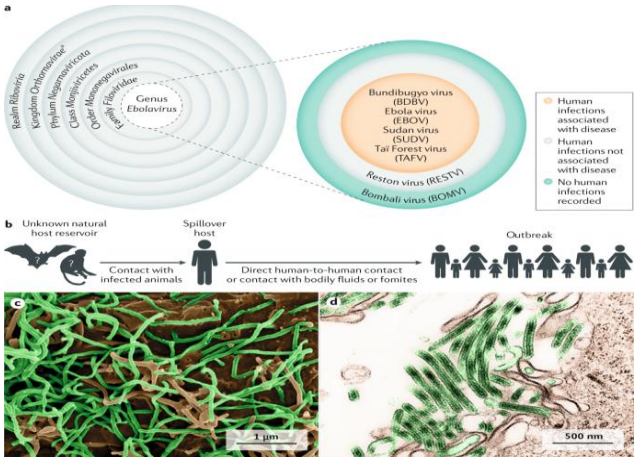

Figure. 1 | Filovirus taxonomy and Ebola virus transmission. **a** | Taxonomy of the Ebolavirus genus. Four of the five *ebolaviruses* that have been linked to human infections thus have been identified as pathogens. **b** | It is still unknown which hosts the EBOV naturally inhabits. Numerous pieces of evidence point to the direct or indirect involvement of bats in EBOV ecology, but to this point, EBOV has not been isolated from and no wild animal has been found to contain a nearly complete EBOV genome[6]. However, given that retrospective epidemiological studies have frequently been able to identify the likely index cases of EVD outbreaks, it is tempting to assume that EVD is a zoonosis (that is, an infectious disease caused by an agent transmitted between animals and humans). These people had interacted with animals in the wild or handled the body of a potential unintentional EBOV host[7,8]. **c** | EBOV particles (green) seen in a scanning electron microscopic (SEM) image as they emerge from grivet cells. **d** | EBOV particles (green) budding from grivet cells are visible in this transmission electron microscopic (TEM) image[9,10]. The International Committee on Taxonomy of Viruses (ICTV) has approved the kingdom name, but it has not yet been ratified. Parts **c** and **d** courtesy of J. Wada and J. Bernbaum, NIH/NIAID Integrated Research Facility at Fort Detrick, Frederick, MD, USA

clinical signs and symptoms

Patients with EVD typically experience symptoms between 2 _ 21 days after an incubation period of 4 _ 10 days[11,12]. The illness can quickly progress into a severe state with a rapid clinical decline after a sudden onset of "flu-like" symptoms (fever, myalgia, chills), vomiting, and diarrhea. Potential hemorrhagic complications and multiple organ failure define this stage of the disease[11,13]. Patients with EVD may experience gastrointestinal symptoms like nausea, stomach pain, vomiting, and diarrhea as well as neurological symptoms like headache, extreme weakness, and coma. They may also experience respiratory symptoms like coughing, dyspnea, and rhinorrhea as well as generalized symptoms from cardiovascular system failure like shock and oedema. Fever along with anorexia, asthenia, and a maculopapular rash between days 5 and 7 after the start of the disease are the symptoms that are most frequently mentioned[12-14]. however, the primary clinical manifestation of the current outbreak is gastrointestinal. Laboratory chemical tests and clinical symptoms both support multi-organ involvement. Leucopenia and lymphopenia are the most prevalent hematological changes, with a specific decrease in neutrophil count and an increase in liver enzymes. Prothrombin time and activated partial thromboplastin time lengthen as the disease progresses in EVD patients, causing thrombocytopenia. The increase in fibrin degradation products and the lengthening of clotting times point to a consumptive coagulopathy brought on by disseminated intravascular coagulation, which worsens multi-organ failure. Most fatal EVD cases pass away between days 6 and 16 following the onset of symptoms. Shock, haemorrhage, and multi-organ failure all result in patient death[14]. If patients recover, clinical improvement and the emergence of the antibody response happen at the same time. The antibody response can occasionally be absent in fatal cases[15,16]. Although the long-term effects of EVD have not been thoroughly researched, the literature that is currently available indicates that patients who have recovered from EVD may experience long-term symptoms and disorders like recurrent hepatitis, myelitis, prolonged hair loss, psychosis, and uveitis[11,13,14].

Diagnosis

By using real time PCR (RT-PCR) to detect the viral genome, acute EVD can be diagnosed. In both fatal and non-fatal cases, the virus is typically detectable 48 hours after infection. This means that EBOV infection cannot be ruled out by a negative test result within the first 48 hours of exposure. Serology is not used to diagnose acute EVD patients due to the rapid progression of the disease, but it may be useful in epidemiological and surveillance studies. IgM antibodies can typically be found starting two days after the onset of the first symptoms and disappear after 30-168 days[17]. The IgG response typically begins between days 6 and 18 after the onset of the illness and lasts for years. When compared to those who survive, the antibody profile of the sera from patients with fatal diseases is noticeably different. Since antibody responses between lethal and survivor cases strongly differ, and it has been demonstrated that deceased patients show a much lower or even absent antibody response compared with survivors[18,19], this difference can serve as a prognostic marker for the management of the patient. T43 FVD outbreaks have been documented in or exported from Africa since the discovery of filoviruses in 1967 (with the exception of at least five laboratory-acquired infections[20,21]). An outbreak, according to epidemiology, is defined as one or more cases that exceed the known endemic prevalence. For instance, the lone case of TAFV infection discovered in a place (Côte d'Ivoire) where FVD had never been reported before is still regarded as an outbreak[22]. With the exception of the TAFV-related outbreak, all FVD outbreaks were characterized by incredibly high case-fatality rates (CFRs, also known as lethality). The largest outbreak up until 2013 was brought on by SUDV and consisted of 425 cases and

224 fatalities (CFR 52.7%)[23]. The systematic study of clinical FVD in humans has been hindered by the generally low number of FVD cases (1967–2013: 2,886 cases, including 1,982 deaths), the typical remote and rural locations of outbreaks, and the frequently delayed announcement of new outbreaks to the international community[24]. Therefore, the commonly used description of FVD was derived either from observation of small groups of patients in care settings that were underequipped for diagnosis, treatment, and disease characterization, or from observation of even smaller samples, like people who were transported from Equatorial Africa to Europe and the USA or who became ill in Europe or the USA after contracting the virus elsewhere. Autopsies have only occasionally been used to characterize the pathology of FVD[24–25]. In the absence of extensive human clinical data, FVD could only be defined further via the use of experimental animal infections [26–27].

Risk elements and outcomes

Age, sex, and ethnicity are examples of demographic risk factors for EBOV infection and subsequent development of EVD that are not well understood. According to current (albeit incomplete) knowledge, sex differences in susceptibility have not been identified, but women who provide care may be more susceptible to EBOV exposure, and the incidence of EVD rises nearly linearly with ageing, peaking at 35 to 44 years. Children typically make up a small proportion of EVD cases, but their incubation times are shorter and their disease progresses more quickly. Children under the age of five have the highest mortality risk compared to older populations[28-31]. Differences in susceptibility across age groups and behavioral factors, such as intentional avoidance of contact with infected people, are potential explanations for the low incidence of EVD in children[30,32]. There have been isolated cases where increases in the incidence of EVD in children have been linked to malaria outbreaks and are most likely the result of nosocomial infections[33].

Molecular level classification

The families *Filoviridae* and *Rhabdoviridae* were split up in 1982 due to the distinctive morphological, morphogen, physiochemical, and biological characteristics of MARV and EBOV (Fig. 2). At the end of the 1980s, work on the molecular characterization of EBOV began. Surprisingly, the first complete genome sequence of a filovirus—MARV—was published despite all of the focus on EBOV. Full-length sequences for two MARV isolates, the *Mayinga* strain of ZEBOV, the Philippine and Pennsylvania strains of REBOV, as well as other viruses are currently available (Fig. 2).

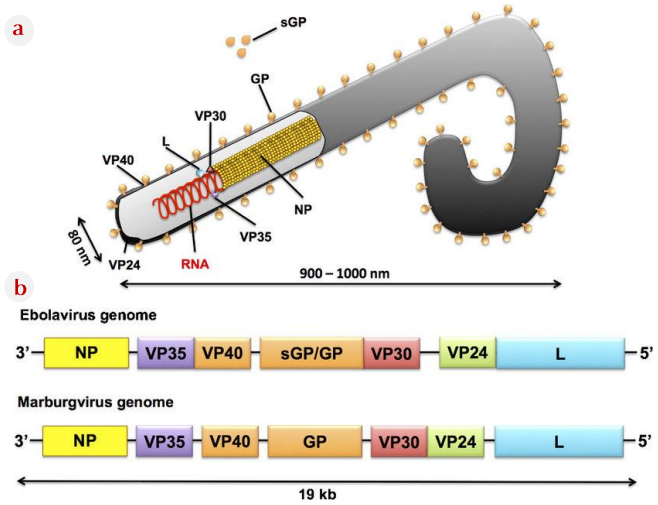

Figure 2 | Filovirus particles.
a | A particle is shown schematically. The polymerase or large (L) protein, nucleoprotein (NP), virion structural protein 30 (VP30), and VP35 are the four proteins that contribute to the formation of the ribonucleoprotein complex (RNP). The carboxy-terminal portion of the glycoprotein (GP), a type I transmembrane protein, anchors the protein to the membrane of the virion. The spikes on the virion's surface are created by homotrimers of GP. VP40 and VP24 are membrane associated proteins **b** | The genome of the Ebola virus (EBOV) is shown schematically. One linear, negative-stranded RNA molecule makes up the genome. The creation of the EBOV infectious clone represented a field-defining scientific achievement[34,36] (Fig. 2).

This accomplishment must be credited to the knowledge attained through research using artificial minigenome systems. An editing site mutant was produced by the infectious clone system, which resulted in the overexpression of transmembrane GP and the loss of soluble glycoprotein (sGP) [34]. The recombinant virus produced less virus but had a greater cytopathogenic effect, showing that RNA editing is necessary to lessen the cytotoxicity of transmembrane GP[34,35]. The role of proteolytic cleavage for the activation of transmembrane GP was investigated using a slightly different and independently developed system[36,37]. Proteolytic cleavage is not necessary for infection, according to a recombinant virus that was discovered and demonstrated to be contagious in tissue culture[36]. This virus expresses non-cleaved GP molecules on its surface. Future research on protein function, genome transcription and replication, pathogenesis, and the development of therapeutic and preventative interventions will benefit greatly from the use of the infectious clone system.

Hypothesis about pathogenesis

Even though significant scientific advances have been made in the past, we still know very little about how EBOV causes disease and how the host immune system responds. According to reports, EBOV has the highest CFR for viral hemorrhagic fevers (up to 88%) and is known to cause the most severe form of hemorrhagic disease in both humans and non-human primates. In addition to immunological and vascular abnormalities, the illness is brought on by a virus that exhibits significant replication. This makes it both an

immunological syndrome and a vascular disease brought on by a virus. Infection with EBOV is linked to fluid distribution issues, hypotension, coagulation issues, and bleeding, which ultimately lead to the abrupt onset of severe shock, just like with some other viral hemorrhagic fevers. Therefore, EBOV haemorrhagic fever can be likened to a state that is triggered by systemic cytokine therapy or brought on by an endotoxin[38]. Case definition and laboratory testing, often real-time reverse transcription PCR to identify viral RNA or quick diagnostic tests based on immunoassays to detect EBOV antigens, must be used in conjunction for the diagnosis. The recent clearance of an EBOV-targeted vaccination by European and US regulatory bodies is the consequence of recent developments in medical countermeasure research. The understanding of EVD and viral persistence in survivors of EVD has significantly improved as a result of new observations arising from the unprecedented (and largest in history) Western African EVD outbreak that occurred from 2013 to 2016 and the ongoing EVD outbreak in the Democratic Republic of the Congo. This has led to the development of new strategies for infection prevention, clinical management optimization, acute illness outcomes, and patient clinical care needs.

Disease progression and transmission

After infection, the interaction between the virus, host, and environment leads to the development of the disease. The four human-pathogenic Ebolaviruses have documented CFRs that differ from one another. The CFR for EBOV varies between 50 and 90 percent of EVD cases[39]. The CFR for the present epidemic is expected to be approximately 50%, however there is some indication that intensive symptomatic therapy can improve results[40]. There is evidence of variances in the CFR for various EBOV species, but it is difficult to interpret this information since it depends on reporting, which may not be ideal[41]. Ebolaviruses can enter the human body through mucosal surfaces, skin abrasions and lesions, or by being passed directly from parent to child. Although not completely precluded, infection through undamaged skin is thought to be uncommon. Successful isolation of the virus from bodily fluids and skin (biopsy) has been accomplished[42]. Infections linked to laboratories have been documented throughout the past few decades, frequently following needle stick injuries or direct contact with infected materials[43]. In the early EBOV epidemic in 1976, CFR after transmission via injection was 100% vs 80% in contact exposure cases[14]. This suggests that the method of transmission may have an impact on the severity of the disease. This has been validated in a non-human primate model, which demonstrates that animals infected through injection develop the illness more quickly than those exposed to an aerosol challenge [44]. Due to the high CFR in EVD and the potential use of EBOV as a biodefense weapon, the pathogenesis of EVD has been relatively well studied during the past 15 years[45].The majority of investigations have been carried out using in vitro, rodent, guinea pig, and primate models. The most pertinent information on human disease comes from non-human primate studies because the virus needs to evolve to cause sickness in rodent and guinea pig experimental research models[46]. The ability of EBOV to infect several cell types after entrance has been demonstrated. Infected immune cells (macrophages, monocytes, and dendritic cells), epithelial and endothelial cells, fibroblasts, hepatocytes, and adrenal gland tissue were found in postmortem analyses of humans and experimentally infected animals. A quick and high peak viremia is the result of extraordinarily effective replication in infected cells[47]. Additionally, it has been suggested that the signs and symptoms experienced by EVD patients may be significantly influenced by the cell death of infected cells, such as the immune system's reduced capacity to fight the infection as a result of necrosis of infected lymphocytes or the reduction in clotting factor production as a result of the loss of hepatocytes[14].

Treatment

According to the WHO, it is moral to utilize experimental medications for the treatment and prevention of EVD given the scope and severity of the present outbreak. Table 1 lists the most promising investigational drugs that have EBOV activity along with the amount of information that is currently available from preclinical and clinical studies that have been published in scholarly publications. Some EBOV outbreak sufferers are being treated with ZMapp, a mixture of monoclonal antibodies. Since effectiveness data on people have not yet been published, its significance in the treatment of EVD needs to be determined. The non-human monkey studies in which ZMapp was able to reverse advanced EVD when given up to five days after infection provide the best evidence yet that it is actually useful in treating EVD[48]. Unfortunately, there isn't much ZMapp available right now. Only the nucleoside analogue favipiravir has undergone extensive testing in humans among the non-antibody based antiviral medicines. Recently, the medication was given the go-ahead in Japan for use in treating people who have new or reemerging influenza viruses. This medication has demonstrated efficacy against a wide range of RNA viruses, including Ebolaviruses, in addition to activity against influenza virus infection[49,50]. When administered six days after infection, favipiravir saved the lives of EBOV-infected mice[51]. Although these findings are encouraging, they still need to be verified in a non-human primate model. Additionally, BCX-4430, a nucleoside analogue with broad-spectrum anti-RNA viral action, has shown promise against the MARV in non-human primates and the Ebola virus in mice[52]. Finally, two drugs being developed to treat EVD are TKM-ebola and AVI-6002, both of which work by silencing genes.

Table 1. Ebola virus sickness experimental cures

Drug	Mode of action	*In vitro* data on Ebola	Non- Non-primate animal data on Ebola	Primate data on Ebola	Drug tested in humans	Drug tested in Ebola infected humans	Approval status
T-705 Favipiravir (Fujifilm Holdings Corp)	Lethal mutagenesis or termination of the RNA chain	EC50 is indeed 31-63 mg/l[53] and IC50 is 10 mg/l[55].	Yes 100% of the mice infected with Ebola survived when given 300 mg/kg/d starting an hour after infection[53]100% of the mice infected with Ebola survived when given 300 mg/kg/d starting six days after infection [55].	At USAMRIID [personal communication M. Koopmans and S. Gunther] currently.	Influenza phase 2 is over, while phase 3 is still running (influenza)	No	New and reemerging influenza viruses accepted in Japan[54]
TKM-Ebola (Tekmira Pharmaceuticals Corp)	Gene silencing	Yes	Yes, TKM-Ebola began one hour after infection, and 3/5 guinea pigs survived (2 deaths unrelated to Ebola) [57]	Yes TKM-Ebola started 30 minutes post infection resulted in survival of 6/8 rhesus monkeys (2 Ebola related deaths)[56]	Phase-1 study partially on hold	No	Not approved
BCX-4430 (BioCryst Pharmaceuticals)	RNA chain termination	Yes EC[55] 3,4 – 11,8 microM	Yes	No, but activity against Marburgvirus in cynomolgus macaques[58]	No	No	Not approved
AVI-6002 (Sarepta Therapeutics)	Phosporodiamidate morpholino oligomer – Ebolavirus specific compound	Yes[59]	Yes	Yes AVI-6002 started 30-60 minutes post infection resulted in survival of rhesus monkeys in dose dependent manner (5/8 survived using high dose)[60]	No	No	Not approved
ZMapp (Mapp Biopharmaceuticals)	Most likely virus neutralisation	Yes	Yes	Yes, when provided up to five days after infection, Zmapp is able to reverse advanced EVD. It can also prevent mortality in cynomolgus macaques when begun within 24 to 48 hours of infection [61,62].	Currently being used to treat small number of victims of the current EBOV outbreak	Yes	Not approved

Conclusion

Clinicians working with returning travellers from the epidemic areas should be more vigilant due to the current EBOV outbreak's rapid and widespread geographic expansion. The initial non-specific EVD presentation, along with a fever and/or other EVD symptoms combination of high-risk exposure (contact with EVD patient or body fluids, wild animals, attendance at a funeral, visit to a local hospital) and symptoms (such as nausea, flu-like illness, headache, diarrhea, myalgia, conjunctival effusion, and redness of the oral and pharyngeal mucosa It is sufficient to continue with isolation and management procedures in patients who visited endemic regions in the previous 21 days if they have a facility or have prepared and/or consumed bush meat. Currently, treatment methods only use beginning supportive care early, where aggressive fluid Replacement treatment has been shown to significantly enhance the mortality rates. specific EVD antiviral management techniques are still in the testing stage. The existing EVD Ebola strains the already strained healthcare and public systems. health care programmes in the afflicted nations, as well as causes greater understanding in nations at risk of EVD import cases. countries and clinical data related to the current epidemic Centers need to be aware of the possibility of receiving a patient with EBOV.

Review Highlights

What Is Already Known?

An early and accurate diagnosis of Ebola is important to help prevent the spread of the disease. But because early symptoms are similar to those caused by other common diseases, it can be hard to diagnose Ebola quickly.

What This Study Adds?

Currently, treatment methods only use beginning supportive care early, where aggressive fluid Replacement treatment has been shown to significantly enhance the mortality rates.

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Conflict of Interests

The authors declare that they have no conflicts interest.

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