Review Article

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Ebola virus disease: epidemiology, clinical feature and the way forward

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ABSTRACT

The Ebola virus disease is a zoonotic, acute viral syndrome which occurs by infection with one the strains of the *Ebola virus*. It is primarily endemic in Africa however the recent outbreak in the year 2014 spanned from West Africa all the way to Europe and America. This shows the virus possess a global threat and should not be considered localized to only certain parts of the world. The social and economic impact of zoonotic diseases today is high as 80% of human pathogens are of zoonotic origin. Human to human transmission happens when there is contact with bodily fluids of infected humans during the infectious phase of the disease. This spread could be through nosocomial means or community spread. Poor knowledge of the syndrome among health care workers coupled with lack of funding and deficient resources has crippled their ability to diagnose and break the chain of transmission of the disease at its early stages. The virus undergoes pathogenesis by immune evasion, immune suppression, coagulopathy, and hypovolemic shock, multiple organ failure and death in up to 90% of cases. The unavailability of a cure or vaccine for this syndrome makes it a recurrent threat due to high risk behavior practiced in endemic countries such as bush meat consumption. Thus this study gives the reader a review of current literature on this deadly disease with the aim of increasing knowledge and aiding its prevention and control.

Keywords: Ebola virus disease, Ebola hemorrhagic fever, Zoonotic diseases, Filoviridae, Communicable disease

INTRODUCTION

The Ebola virus disease (EVD) is a zoonotic, acute viral syndrome which occurs by infection with one the strains of the *Ebola virus* (EBV). According to the International Committee on Taxonomy of viruses, the EBV is a non-segmented, enveloped, negative sense, single stranded RNA virus. As a re-emerging zoonotic disease, the EVD has been involved in about 25 outbreaks worldwide. The disease is primarily endemic in Africa however the recent outbreak in the year 2014 spanned from West Africa all the way to Europe and

America.^{7,8} A lesson to learn from this is that these pathogens should not only be considered restricted to certain parts of the world.^{9,10} Therefore, without preemptive measures in place they could easily board a flight and spread across continents causing chaos in a matter of hours with an example being the case of a Liberian immigrant to Nigeria.^{9,11,12–14} The social and economic impact of zoonotic diseases today cannot be over emphasized as about 80% of human pathogens are reported to be of zoonotic origin and thousands of deaths have been associated with them in recent times.^{8,15}

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The virus is highly infectious and can be transmitted from one host to another in a short time through contact with infected bodily fluids and secretions of both living and dead people. ¹⁶ Unsupervised hunting of wild animals for bush meat consumption which is highly practiced by communities in parts of Africa are major factors contributing to the initiation as well as spread of zoonotic diseases like these. ^{17,18} Parts of the world mostly affected by such diseases usually have pre-existing problems in the health care sector such as poor funding as well as deficient, over populated and ill equipped health care facilities mostly due to a failure of government. ^{19,20} This makes prevention and control of such diseases quite difficult especially in communities where high risk behaviors are part of their culture and tradition. ¹⁸

Nosocomial spread of the disease has been its major mode of human to human transmission, and this has largely been attributed to poor knowledge of the virus and the inability of health care workers (HCW) in affected regions to identify the disease in its early stages where it presents with non-specific symptoms similar to other infectious diseases endemic in the regions. ^{13,14,21,22–26} This makes this disease a significant threat and a major public health problem not only to endemic countries but to the world at large. ^{9,27}

EPIDEMIOLOGY

The initial outbreaks of the EVD were first noticed around the same time in the regions of Southern Sudan and Zaire of Africa around the year 1976. The first documented outbreak occurred as a result of poor infection control practices in the clinics where unsterilized needles were being used on multiple patients.¹⁸ The clinical presentation at the time were similar to that of malaria parasite infection; however later on a pathogen was isolated in blood sample which yielded the now known as EBV named after a small river near the northwestern part of Democratic Republic of Congo (DRC). The Sudan and Zaire Ebola virus species were found to be implicated in these initial two outbreaks. The Tai Forest Ebola virus was discovered in the Tai forest reserve of Cote d'Ivoire in 1994. It was isolated from the blood of a Swiss biologist who acquired the infection while performing necropsy on a chimpanzee residing in an area where people had recently died due to what was suspected to be EVD. 1,9 Monkeys being transported from the Philippines to Reston, Virginia USA in November 1989 were later found to be infected and lead to the discovery of the Reston Ebola virus species. This specie however, has so far been identified as nonfatal to humans.^{1,9} The latest discovery among the five species is the Bundibugyo Ebola virus which was involved in an outbreak in Uganda around the year 2007-2008, and subsequently followed by another in DRC in the year 2012. 1,9 Studies have reported the Zaire Ebola virus to be implicated in the 2014 West African outbreak.²⁸

CLINICAL FEATURES

Pathophysiology

According to the International Committee on Taxonomy of viruses, EBV is a non-segmented, enveloped, negative sense, single stranded RNA virus.³ It belongs to the order Mononegavirales and family called Filoviridae, which also comprises of the genus known as Filovirus. In this genus are morphologically similar but serologically different species known as EBV, Marburg Virus (MARV) and Cuevavirus. 1,2 According to Wong and Wong, the name filovirus describes their morphologically filamentous appearance having an approximate diameter of 80 nm, and a length which ranges from 800-14000 nm. With a size of approximately 19 kb, the EBV and MARV are made of seven genes which are Nucleoprotein (NP), VP35, VP40, Glycoprotein (GP), VP30, VP24, RNA-Dependent RNA polymerase, and also an eighth called smaller Glycoprotein (sGP) unique for the EBV which it secretes extracellularly. These genetic proteins have been found to play a key role in its virulence by inhibiting the host immune system.^{3,9} These filoviruses are able to withstand temperatures up to 20° C and still do not desiccate and this is a likely reason why they are stable in aerosol droplets; however, they are easily inactivated by common substances such as household detergents, phenolics and hypo chlorides.9 Rajak et al stated that there are five different strains of the EBV which are known to cause infection in both human and non-human primates. They are the Zaire ebolavirus, Sudan ebola virus, Bundibugyo ebolavirus, Reston ebola virus and the Cote d'Ivoire ebolavirus (now known as Tai Forest Ebola irus). 18 The Zaire, Sudan and Bundibugyo Ebola viruses have been involved primarily in large outbreaks around the Central African tropical rain forest, and also West African distant villages. Reston Ebola virus however so far is not linked to any human deaths but is known to be fatal to Chimpanzees, Gorillas and monkeys 18 while the Tai forest Ebola virus has recorded only one human death. 1,18

Life cycle

The life cycle of the EBV has six phases which are attachment, penetration, un-coating, maturation and delivery.²⁹ The first stage of its life cycle begins when GP1 (a component of GP) attaches itself to the hosts cell surface receptors, these may be dendritic cells, liver, spleen, T cell immunoglobulin and Mucin however there is still no clear evidence which of these is most preferred.²⁹ After successful attachment, the virus penetrates the host through two processes, which are micropinocytosis and clathrin mediated endocytosis. 1,29 At this stage when entry has been achieved the virus is then transported into the endosome where it attaches itself to the endosomal membrane by the resence of several factors such as GP.1 Viral replication and transmission then takes place in the host cell cytoplasm with the aid of VP35, VP30 and RNA dependent-RNA

polymerase.²⁹ Maturity is achieved by the role of VP24 that is important for both cell assembling and nucleocapsid formation.²⁹ Around the same time, GP undergoes some form of modification in the golgi apparatus then later moves to the cell membrane.^{1,29} The final stage is viral budding and release which is primarily the role of VP24.

Mode of transmission

This transmission of the EBV from one host to another can only be possible when the virus makes contact with mucosal surfaces or exposed barriers such as a wound or broken skin.^{9,28} This transmission can occur through several channels and across multiple hosts as shown in Figure 1. Spread of the virus can occur either through epizootic or via human to human transmission. Epizootic transmission of the pathogen occurs from its natural reservoir to other non-human primates (such as gorillas, chimpanzees, baboons, African green monkey). Details of how this virus gets from this primary reservoir to other primates is still not known. 18 Although the fruit bat is regarded as the primary reservoir of the EBV, there is still no proven evidence to substantiate this. 16 Primary human transmission occurs when humans make contact with infected body fluids of wild animals in the process of transportation or during preparation for bush meat consumption as has been documented in DRC, Uganda and Gabon.18

Human to human transmission happens when humans make direct or indirect contact with bodily fluids of other infected humans during the infectious phase of the disease. This has so far been the major route of spread of the disease, and could either be through nosocomial means or through community spread. Nosocomial or hospital acquired infections often occur when there is poor compliance with universal precaution among HCW. Health care centers have played a role in multiplying the rate of spread of EVD in the recent outbreak. The multiple use of unsterilized equipment has been implicated in initiation of the spread of EVD in the first outbreak at 1976 DRC. Lack of use of Personal Protective Equipment (PPE) has also lead to many health care personnel contracting the virus. 119

Ftika and Maltezou, 2013 made an investigation and analyzed information dating back to the 1976 outbreak; they reached a conclusion that nursing a patient without the proper PPE had a transmission risk ratio of 81%. This was consistent with the findings of Baron et al whose study was of the South Sudan EVD outbreak in the year 1979. He found in his study that 24 out of the 36 (67%) people who nursed an EVD patient got infected while only 13% of those reported to have only casual physical contact contracted the disease. ¹⁶ There have also been reports of accidental occupational exposure in laboratory workers when performing certain investigations on infected samples. Overall, the spread of the infection has

been found to multiply where universal precaution is ignored in somewhat poor health facilities. ¹⁸

Community spread of the virus has been a major problem and probably even more difficult to control than nosocomial spread. Wong and Wong, 2015 stated in their study that during the 1995 outbreak in Kitwit about 80% of those that contracted the virus were through community spread. Burial traditions in these countries such as unprotected washing of dead bodies have been known to further escalate this epidemic. 18 Sexual intercourse and breast feeding are also not to be left out as studies have shown that the virus is able to remain in secretions such as semen and breast milk for more than 90 days to 4 months. 9,32,33 Therefore, it is advisable that survivors of EVD should refrain from both sexual intercourse and breast-feeding until the above window period has elapsed. There have been no documented cases of aerosol transmission of EVD in humans, although in non-human human primates there have been reports of infection after inhalation of droplet sizes ranging from 0.8-1.2 micrometers.^{9,33}

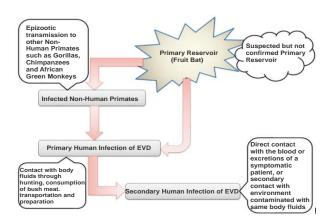


Figure 1: Mode of transmission of the *Ebola* virus disease.

Pathogenesis

These pathogens mostly gain entry into a host by contact with broken skin, through mucous membranes or also through iatrogenic means by the use of infected and unsterilized equipment. 18,34 It has affinity for a variety of cell types including but not limited to monocytes, macrophages, dendritic cells, fibroblasts, hepatocytes, adrenal cortical cells and epithelial cells but the first point of replication is monocytes, macrophages and dendritic cells.³⁴ After replication in these cells, lymphatics and blood flow aid in transporting the virus to the liver, spleen and lymph nodes known collectively as the reticuloendothelial system. ^{9,29} They then further multiply and cause severe damage and cell death in these organs. The virus is able to multiply and reach high levels with the help of VP35 and VP24 genes that interfere with the interferon pathway at different stages, this interferon pathway helps in preventing viral penetration into cells

and form a major defense mechanism against viruses (To et al). Therefore, its failure would mean vulnerability of the hosts defences. The virus also destroys lymphocytes by a mechanism called the "bystander apoptosis mechanism" while sparing cells such as macrophages, monocytes, dendritic and endothelial cells.³

While these events are occurring, the cytokines released from the site of infection cause further influx of macrophages leading to more apoptosis and paving the way for the virus to further multiply in the blood stream.³⁵ This inflammatory response leads to a rise in interleukins 2 and 10, TNF, interferons alpha and gamma causing micro vascular damage, increased vascular permeability, vasodilatation which manifests as both internal and external bleeding.^{3,9,35} Furthermore, liver infection and damage results in failure of homeostasis mechanism, secondary bacterial infection and abnormal release of nitric oxide.^{1,35,36} The eventual outcome of all of these events put together is severe shock, disseminated intravascular coagulation, multiple organ failure and death in most cases.³⁶

Signs and symptoms

The disease has an acute onset involving many systems in the host.²⁹ After an incubation period of about 2-21 days, EVD is characterized by early non-specific symptoms which may resolve in some survivors, or may progress to a full blown hemorrhagic syndrome. 9,28,37 In the early stages of the disease it is characterized by constitutional symptoms which make it's diagnosis even more difficult.²¹ The first symptom which manifests is fever of >38°C in about 85-95% of patients, this is the most common symptom followed by other non-specific symptoms such as headaches (52-74%), general malaise (85-95%), difficulty in swallowing and sore throats (56-58%), while about 26% of patients experience dry cough. 9,27 As the infection progresses after a few more days, more serious symptoms manifest such as pain in the abdomen noticed in 62-68% of patients, muscle pain (50-79%), nausea, vomiting and also diarrhea in 84-86% of patients.9 In patients that progress to develop the full syndrome, hemorrhagic symptoms begin to appear at the late stage of the disease. Patients start to bleed from several orifices, about 11% of patients develop hemoptysis, hematemesis (0-13%), nose bleeding (2%), blood in the urine (7-16%) and bleeding at venipuncture sites in about 5-8%.

After about one week of manifestation of symptoms, physical examination may reveal signs such as diffuse red rashes widely distributed across the body excluding the face in about 16% of patients. There is also redness of the conjunctiva, tenderness of the abdomen and general signs of dehydration. At When the disease progresses to the hemorrhagic phase, red spots called petechiae are seen in about 8% of patients; intra-oral examination reveals bleeding gums (18%), frank blood appearing in stool (8-16%) with urinalysis showing blood in urine

(16%).^{1,27,36} However these classical signs of viral hemorrhagic fever are only exhibited by about 40% of patients.⁹ Similarly, it is reported by Meyers et al, that studies carried out in 1995 at DRC on EVD patients demonstrated that only 41% of them showed signs of bleeding.

DIAGNOSIS

Rajak et al, reported that a major problem in Ebola outbreaks is late diagnosis due to a lack of knowledge and familiarity of clinicians with the disease as well as a variety of non-specific symptoms in its presentation. Also during the 2014 outbreak, the spread of the disease in Guinea has been attributed to wrong diagnosis of the initial cases by the HCW. Early diagnosis of EVD is a vital skill in the effort to put in place early prevention and control measures before it is too late. Certain risk factors established in the history of a patient as well as a thorough examination can serve as pointers and aid in reaching a provisional diagnosis. However, EVD is difficult to diagnose by clinical assessment alone. A case is confirmed only when laboratory results are positive which is often delayed especially in poor resource settings. The service of the diagnose of the diagnose of the disease in Guinea and the diagnose of the diagnose of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disease in Guinea has been attributed to wrong diagnosis of the disea

The confirmation of the disease can only made by laboratory tests on blood samples in bio-safety level 4 laboratories. ^{27,29} The WHO in 2014 advised that samples should only be collected at appropriate facilities called Ebola treatment Centers (ETC), they also recommended whole blood or oral swab as samples for specific investigations.³⁸ Reverse transcriptase polymerase chain reaction (RT-PCR) and enzyme linked immunosorbent assay (ELISA) are currently most widely used for laboratory confirmation of the EVD. 27,39 RT-PCR detects viral RNA in blood samples of infected patients, it is able to do this as early as immediately after the initiation of symptoms^{27,40}. This is currently recommended for use because of its several advantages such as high sensitivity of up to 100% reported in recent studies as well as early detection of the virus. It is also most suitable when there is an epidemic because results can be ready in approximately 24-48 hours.²⁷ ELISA detects the immunoglobulins G and M in samples of infected patients however, a problem with this technique is that it is not as sensitive (91%) as RT-PCR and secondly the Immunoglobulins appear much later in the stages of viremia which makes it a less recommended method for early confirmation during an outbreak investigation.^{27,29}

MANAGEMENT

There is still no cure for the EVD therefore management of EVD is mainly by supportive therapy; this gives the immune system enough time to re-mobilize and combat the pathogen. ^{1,37} This is done through respiratory support, correction of fluid and electrolyte balance and treating coagulopathies alongside others. ^{1,27} Other pathologies such as fall in hemoglobin levels and hemorrhagic

symptoms can be corrected by the use of cryoprecipitate, prothrombin complex concentrate as well as plasma. 41,42 According to the WHO, for an EVD patient to be discharged all signs and symptoms must resolve plus a negative laboratory test such as RT-PCR for viral RNA sometimes on two different occasions. 43

PREVENTION

The center for disease control (CDC) has several recommendations for primarily preventing transmission of the EVD such as hand washing and good personal hygiene, avoidance of contact with secretions of infected patients, avoidance of unsupervised burials of dead patients, use of PPE for HCW and proper sterilization and disinfection of reusable equipment among others. Secondary transmission of the disease can be prevented by immediate isolation of confirmed cases, thorough contact tracing as well as quarantine of suspected cases. Vaccination is the best form of prevention of infectious diseases however, a vaccine is still currently not publicly available for the EVD although current trails show positive results. 37,47-49

CONCLUSION

The EVD is a highly fatal disease which is endemic in Africa however recent experience has shown the pathogen to be a global cause for concern. The virus is highly transmissible from infected body fluids of living as well as dead patients. Its similar signs and symptoms at the early phase with other infectious diseases in endemic regions coupled with poor knowledge among HCW makes early diagnosis difficult. The unavailability of a cure for this deadly disease means any future outbreaks could result in more deaths if pre-emptive preventive measures are not in place. Although current vaccine trials show a high potential for success; its accessibility, distribution as well as ensuring compliance and acceptability among recipients in local communities may take years to accomplish. This might be too long especially for a disease that spreads so fast with high fatality rates. Therefore, knowledge is currently the fastest, cost effective and easiest mode of prevention. If this is properly harnessed and trickles down to the grassroots and community level, it could serve as the final nail in the coffin for this pathogen which is so far under control.

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