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Ebola's Fatal Hemorrhagic Fever from Discovery to Vaccine

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Abstract

The Ebola Virus (EBOV) causes a hemorrhagic fever that is distinguished by a sudden onset of intense headaches, fever and severe hemorrhages which can be fatal in less than a week. The largest Ebola outbreak to date is currently underway, with 28.488 confirmed, probable and suspected cases reported, 15.239 laboratory confirmed cases and 11.297 fatalities as of October 11th, 2015. Most of the cases have occurred in Sierra Leone, Liberia and Guinea. The Ebola virus genus has five species: Zaire, Sudan, Tai Forest, Reston and Bundibugyo. The Zaire virus has caused ten epidemics since its identification in 1976, with a mortality rate of 57%-88%. Fruit bats appear to be the natural reservoir of EBOV, while human to human transmission is spread through direct contact of infected bodily fluids; patients only acquire the ability to infect others when symptomatic. Once inside the host, EBOV infects immune system cells directly and begins to replicate inside them while severely compromising it. Recent evidence shows EBOV alters cytokine expression while expressing its own viral proteins causing significant lymphopenia and lymphapoptosis, as well as endothelial damage. Massive hemorrhages throughout the body are one of the cardinal points of EBOV infection; however, it is not as present in patients as it is believed. The current outbreak has affected countries where sanitation is inadequate, resulting in the inability to control its spread. This review aims to give a broad spectrum of the current findings in several fields to better comprehend Ebola´s fatal Hemorrhagic Fever.

Keywords: Ebola virus disease; Hemorrhagic fever; Filoviridae; Epidemic

Introduction

The Ebola virus (EBOV) causes a hemorrhagic fever that is distinguished by a sudden onset of intense headaches, fever and severe haemorrhages which can lead to death in less than a week [1,2]. The largest Ebola outbreak to date (caused by the Zaire Ebolavirus or ZEBOV) is currently underway, with 27.898 confirmed, probable and suspected cases reported up to the 2nd of August of 2015, with 15.213 laboratory confirmed cases and 11.296 fatalities. Most of these cases have occurred in Sierra Leone, Liberia, and Guinea, although there have been isolated incidents in Mali, Nigeria, Senegal, Spain, the United Kingdom and the United States of America. An increase in the incidence rate was reported in Guinea towards the end of March, while Sierra Leone's rate remained stable and Liberia, which has been declared a country with former widespread of transmission and current, established control measures, however on June 29 the last case of Liberia was reported and confirmed [3]. There is still no approved treatment for this disease. The WHO believes that this epidemic's first case (patient zero) was an 18 month old boy who lived in Meliandou, Guinea. The boy became sick the 26th of December of 2013, developing fever, black bowel movements and vomiting, only to succumb to the disease two days later. It is believed he probably became infected after being in contact with some wild animal since he had been playing near a bat infested tree shortly before presenting symptoms. The first Ebola case was identified the 26th of August of 1976 in a small village in the north of the Democratic Republic of the Congo (which was known back then as Zaire). Patient zero was the village's school principal, who likely became infected after walking near the edges of the Ebola river between the 12th and 22nd of August. Two weeks after the beginning of his symptoms, he died the 8th of September. The current outbreak has affected countries where sanitation is inadequate, resulting in the inability to control and prevent its spread. However, thanks to the efforts of several international organizations such as the WHO (World Health Organization) and MSF (Medecins Sans Frontieres), appropriate measures have been implemented to avoid a global health crisis [4].

The Ebola virus belongs to the family Filoviridae, whose virions have a distinctive filament-like shape. However, it is a pleomorphic virus, and therefore can adopt several shapes, reaching lengths of 19,000 nm. Its diameter is typically 80 nm. The virus' genome consists of a lineal molecule of negative single stranded RNA (19.1 kb), whose organization is very similar to the members of the family Paramyxoviridae (which are no segmented negative single stranded viruses) [5-8]. The Ebola virus genus has five species, which are named after the place where they first appeared: Zaire Ebola virus, Sudan Ebolavirus, Tai Forest (Ivory Coast) Ebola virus, Reston Ebola virus and Bundibugyo Ebolavirus [2]. The Zaire virus has caused ten epidemics since its identification in 1976, affecting 30-300 people per epidemic, with a mortality rate of 57-88% [9]. There have been four reported outbreaks of the Sudan virus, two in Sudan in the 1960s, one in Uganda in 2000, and another in Sudan in 2004, with a mortality rate of 50% [10]. However, other sources report a mortality rate of 41%-65% [11]. The Ivory Coast virus has only been identified in one person, who survived the infection [12]. The Reston virus does not

appear to have affected humans, and its reservoir appears to be some animals in the Philippines. The Bundibugyo virus appeared in Uganda in 2007, with a mortality rate of 30%, although other sources mention up to 40% [1,13].

Transmission

The Ebola virus' natural reservoir is still to be determined, although it is thought that infection occurs when people come into contact with certain animal species, whether they are alive or dead. Possible reservoirs include chimpanzees, gorillas, forest antelopes, hedgehogs and fruit bats [3,10,14].

Natural Reservoirs

Fruit bats appear to be the natural reservoir of EBOV, particularly the hammer-headed fruit bat (Hypsignathus monstrosus), Franquet's epailetted fruit bat (Epomops franqueti) and the little collared fruit bat (Myonicteris torquata). These bats are common in Subsaharan Africa and migrate between countries. It is believed that this is how the EBOV got to Guinea. Humans may have been infected by the hunting or eating of these animals, which had been suspected in Gabon [15-19].

The infection by ZEBOV in Epomops franqueti, Hypsignathus monstrosus and Myonectris torquata affects the spleen and liver in 3% of bats, while 7% have IgG against ZEBOV. This is unlike humans, where the virus disseminates to the whole body [16]. Considering this, we can understand how outbreaks occur in the west and east sides of Africa. The asymptomatic host animal migrates across the continent, spreading the virus upon its arrival [20,21]. Epidemiological studies have shown that chimpanzees were the source of infection in the Ivory Coast case in 1994 and in an outbreak in Gabon in 1996 [22,23].

Another study showed that rhesus macaques inoculated with ZEBOV could infect other monkeys in a cage three meters away, without having any direct contact. Transmission probably occurred due to aerosolized droplets that came in contact with the oral, conjunctival or nasopharyngeal mucosa. A similar experiment was conducted using guinea pigs and rhesus macaques, with the same result. The CDC confirmed that five people who came in contact with pigs infected by the Reston virus developed antibodies against it, without ever presenting symptoms [24-27].

Transmission in Humans

The route of transmission of primary infections by Filoviridae in humans is unknown. Secondary infections however, are caused by being in close proximity with infected patients, namely direct contact with their blood, tissues or other bodily fluids. Infection can also occur due to poor handling of a contaminated water source [28,29].

The Ebola virus is spread through direct contact of infected bodily fluids with the patient's own bodily fluids. These fluids include saliva, breast milk, tears, blood, sweat, urine, feces, vaginal secretions, vomit and amniotic fluid. Consequently, the virus may enter through the mucous membranes, through a parenteral route, or through a skin lesion. Another possible route of infection is the ingestion of animals that function as natural hosts [30-33].

A study conducted by Bausch et al. demonstrated the presence of the virus during the acute phase of the disease in a variety of bodily fluids. The virus was detected in the urine, sweat (albeit in low concentrations) and saliva (where it would rapidly deactivate). Hence, infection rates due to fomites, casual encounters and the sharing of toilets are relatively low [33].

ZEBOV has been isolated in the semen of an affected patient using RT-PCR, up to 82 and 91 days after the disease's debut [34]. The Marburg virus has also been isolated in semen and can be transmitted sexually in a period similar to that of ZEBOV. It is believed that the virus is able to survive for longer periods of time in immunologically privileged sites, such as the gonads, mammary glands and eye chambers [35-37]. The presence of ZEBOV in breastmilk increases the likelihood of direct transmission from mother to child. The virus' reportedly low presence in saliva samples may be due to rapid deactivation by enzymes or other substances found in saliva [38]. However, it has been shown that patients with positive saliva samples (determined by RT-PCR) have a higher mortality rate, linked to elevated viral shedding and viremia, which has been identified as a poor prognostic factor [38-40].

Pathophysiology

Once inside the host, the virus faces the first line of defense: The innate immune system. Said line of defense includes polymorphonuclear leukocytes (PMN), dendritic cells (DC) and macrophages (MQ). The virus infects dendritic cells, macrophages and monocytes directly [41]. In the days following the infection, the virus begins to replicate inside these cells. Replication of the Ebola and Marburg viruses has also been seen within endothelial cells, which explains a grand part of its pathogenicity [42-44]. After attacking the dendritic cells, macrophages and monocytes, the innate immune response is severely affected, this is also detrimental to the adaptive immune response [5-7] whilst travelling in the previously mentioned cells; the virus migrates towards secondary lymphoid tissue, gaining access to a whole new repertoire of immune system cells. Filoviruses show affinity for several cells and can eventually be found in several non-lymphocytic cells in advanced stage disease [45-48]. Numerous receptors promote the entry and adhesion of filoviruses, although these mechanisms are still not completely understood. It appears that type C lectins in dendritic cells confer the virus with the ability to attach to specific intercellular adhesion molecule 3 (ICAM3), giving way to the infection mediated by the filovirus' glycoprotein [49]. Furthermore, type C lectins in human macrophages specific for galactose/N-acetylgalactosamine, which are expressed by cells of monocytic origin also promote viral entry. Once infected, the ZEBOV begins using these cells to produce pro-inflammatory cytokines and viral proteins [50]. The viral protein VP35 prevents the production of type 1 interferon (IFN-α and IFN-β) and VP24 interferes with interferons α, β and γ's ability to produce an antiviral cellular state [51,52]. These antagonistic effects against interferons are not only implicated in advanced stages of the infection with high viral loads, but also in early stages regarding the innate immune system's dysregulation. Dendritic cells infected by ZEBOV are incapable of maturing into antigen presenting cells (APCs) and are therefore incapable of activating T lymphocytes. They are also unable to produce a series of pro-inflammatory cytokines which are necessary for T-cell signaling [44,53,54]. Infected monocytes and macrophages are also incapable of producing interferons, but they retain their ability to produce TNF and other pro-inflammatory cytokines. The viral particles are also capable of activating polymorphonuclear leukocytes such as neutrophils to release their preformed granules while also causing them to enter an activated state [42,55,56].

Invasion and Evasion Mechanisms

Several components of the ZEBOV genome have been identified, some of which are: nucleoprotein RNA polymerase, glycoprotein, VP24, VP30, VP35 and VP40. The ones that seem to be the most involved with the virus' pathogenicity are VP35, VP24 and its glycoprotein [57].

VP24

Viral Protein 24 (24 kDA) inhibits the intracellular activity of IFN-α. It blocks the signaling pathway by interacting with karioferin alpha 1, preventing its accumulation within the nucleus [52]. This "blockade" occurs due to the inhibition of transcription factors STAT1 and STAT2, diminishing the expression of type 1 IFN [58]. It also increases the amount of nitric oxide (NO) in a directly proportional fashion [45].

VP35

Viral Protein 35 inhibits the activation of transcription factors IRF3 and IRF7, which act on the innate immune system during its response to the virus. IRF7 acts on type 1 interferon genes, regulating IFN-α genes and possibly activating the enzyme PIAS1, which inhibits the STAT1 mediator gene and its DNA binding capacity, promoting this gene's silencing [59,60]. VP35 can be found within the cytoplasm where it interacts with the SUMO protein, which promotes the ubiquitinization of IRF7 in dendritic cells. It also blocks the recruitment of IRF7 by IFN-α and IFN-β genes [61-63]. It has also been suggested that VP35 suppresses sRNA in endothelial cells, along with iRNA [64].

Interestingly, VP35 causes dendritic cells to express an increasing amount of IL-6, IL-12, TNF-α and type 1 IFN. They also produce less CD40, CD80, and CD86, causing a stall in the cell's maturing process [65-69]. RIG1 is also inhibited by VP35 in dendritic cells, causing interference in the IFN production pathway, apoptosis regulation and a diminished immune response against the virus [70-74].

GP

The glycoprotein has two active forms, the structural glycoprotein or virion glycoprotein (vGP), and secreted glycoprotein (sGP) [75,76]. The vGP forms trimers that bind to endothelial tissue, add themselves to its genome and provoke changes in the infected cell's morphology, causing them to swell and detach from the basement membrane. The vGP's affinity for endothelium is explained by a mechanism similar to one observed in retroviruses known as "pseudotyping". This explains why the vGP is unable to bind in some genetically predisposed patients, whom remain asymptomatic and promote its survival. This provides a unique window of opportunity for the development of targeted treatments [77,78].

sGP

The sGP's toxicity is directly proportional to its quantity. Viral replication occurs initially by this glycoprotein's invasion of endothelial cells due to transfection. These cells are used as viral DNA replication machinery. Afterwards, sGP will also provoke the cell's death, resulting in a massive release of viral copies to keep promoting infection in surrounding cells as seen on Figure 1 and Figure 2.

The damage and loss of these endothelial cells can promote an increase in permeability, exposing the basement membrane and compromising vascular integrity [75–80].

On the other hand, evasion mechanisms include epitope masking and steric shielding of membrane proteins, such as MHC1 and β1 integrin (Figure 1) [81]. These mechanisms entail the occlusion of MHC1 with the glycated portion of the GP. This mechanism is unique to the EBOV [82]. Because of these mechanisms, the EBOV is able to avoid the humoral immune response, since highly immunogenic epitopes are kept from the immune system. Furthermore, the GP prevents adequate antibody production by creating a microenvironment incompatible with their effective production. Therefore it can be said that the ZEBOV also affects the immune response mediated by lymphocytes in an indirect fashion [83-87].

Cytokine storm

The infection by EBOV causes changes in the immune response, expressing different cytokines in an aberrant fashion, generating a cytokine storm which causes lymphapoptosis amongst other cytotoxic effects in different cell lines [88].

Numerous cytokines increase their expression, provoking a recruitment of immune cells and a pro-inflammatory response. Studies vary regarding the amounts of cytokines expressed, with some reporting changes while others report normal levels. The cytokines in Table 1 tend to be affected by the EBOV, causing their levels to either increase or decrease. The main cells affected are macrophages and dendritic cells, which promote and stimulate the maturing and secretion of pro-inflammatory cytokines. No difference has been seen amongst the chemotactic changes between different strains of ZEBOV [88,89].

Increased levels of IL-6, IL-1b, TNF-α, MCP1 and MIP1-α and β have been reported in the first week following infection in humans who become symptomatic. In addition, a higher fatality rate has been associated with increased levels of these cytokines [90-93]. However, asymptomatic patients have shown a disappearance of this response within 2-3 days [94,95].

Cytokine	Function	Change
IL-1B	Produced by activated macrophages, stimulates thymocytic proliferation, inducing release of IL-2, maturing and proliferation of B lymphocytes. Highly involved in pro-inflammatory and pyrogenic processes [96,97]	Increase [44,88,91]
IL1-RA	Secreted by various cell types, including immune cells, epithelial cells and adipocytes. Natural inhibitor of IL-1B [98]	Increase [88,91]
IL-2	Generates tolerance and immunity due to its effect on T lymphocytes. Promotes the differetiation of T lymphocytes into effectors and memory cells after being exposed to an antigen [99]	Increase, normal or decrease [88,91]

IL-3	Immune response, positive regulator of cellular proliferation and myeloid leucocytic differentiation [100]	Decrease [88,91]
IL-4	Activates humoral immunity, inducing the expression of MHCII in B lymphocytes. Amplifies the secretion and expression of immunoglobulins. Promotes isotope change in B lymphocytes. Negative regulation of macrophage activation. Promotes antivirus defense [101,102]	Decrease [88,91]
IL-5	Final differentiation and proliferation of B lymphocytes. Promotes JAK-STAT pathway. Immune response [103]	Decrease [88,91]
IL-6	Secreted by macrophages in response to pathogens. Fever mediator. Important in the acute immune response. Stimulates neutrophil production in the bone marrow and maturing of B cells [104]	Increase [88,91]
IL-8	Neutrophil, basophil and T lymphocyte chemotaxis. Involved in the neutrophil activating process. Secreted by several immune cells in response to an inflammatory stimulus [105]	Increase [88,91]
IL-9	Cellular growth and proliferation. Immune response [106]	Decrease [88,91]
IL-13	Decreases cytokine production. Immune response. Activates STAT6 protein. Proliferation of B lymphocytes. Macrophage activation [101]	Decrease [88,91]
IL-15	Stimulates T lymphocyte and Natural Killer (NK) proliferation. Prevents apoptosis [107]	Increase [88,91]
IL-16	Stimulates CD4, monocyte and eosinophil migratory response. Prepares CD4 cells to react to IL2 and IL15. Induces expression of IL2 receptor in CD4 cells [108]	Increase [88,91]
TNF-α	Secreted mainly by macrophages. Pyrogenic factor. Positive regulator of apoptosis, NO, caspases, Ig secretion, cytokine production, mitosis, caspase activation and fever [109,110]	Increase [88,91,127]
MIP-1a	Monocyte, eosinophil, neutrophil and lymphocyte chemotaxis. Induces inflammatory response. Provokes TNF production [111]	Increase [88,91,127]
MIP-1b	Involved in the viral and inflammatory response, cellular adhesion and cellular mobility. Monocyte and NK chemotaxis [111]	Increase [88,91,127]
MCP-1	Monocyte, basophil, lymphocyte and macrophage chemotaxis. Involved in JAK-STAT pathway. Provokes NO synthesis [112,113]	Increase provokes lymphapoptosis through JAK-STAT pathway [88,91,127]
MCSF	Macrophage differentiation, major role in inflammation, involved in Ras signaling pathway [114,115]	Increase [88,91]
MIF	Inflammation, cellular proliferation, and macrophage activation [116]	Increase [88,91]
IP-10	Chemotaxis of T lymphocytes and NK cells. Proliferation of macrophages and dendritic cells. Involved in the inflammatory response and antiviral defense [117,118]	Increase [88,91]
GRO-a	Neutrophil chemotaxis. Involved in inflammation and induction of cellular proliferation [119]	Increase [88,91]

Table 1: Cytokines involved in the infection by EBOV.

Reactive oxygen species (ROS) and reactive nitrogen species (NOS) production increases within infected cells during the cytokine storm [120]. This event causes an immune unbalance, provoking cytotoxicity and immune cell death at the signaling site. It also causes local vasodilation, increased endothelial permeability and expression of adhesion molecules [121].

The cytokine storm causes several other effects in the body, such as suppressed antiviral immune response (caused by the diminished levels of IL-3, IL-4 and IL-5), macrophage and neutrophil chemotaxis (due to increased levels of MCP-1, MIP-1a, MIP-ß and IL-8), increased cell differentiation (IL-2), and inflammation (IL-1, IL-6, IL-9 and IL-13). It is important to remember that several of these cytokines can cause apoptosis in immune system cells (decreased IL-15 and increased TNF-α, MIP-1a and MCP-1) [41,67,122,123].

Lymphapoptosis

EBOV infection causes significant lymphopenia at increased viremia levels, as well as during an extensive cytokine storm [67,124].

The EBOV does not interact directly with lymphocytes as it does with macrophages and dendritic cells, but it affects them indirectly due to the effects of the cytokine storm [125,126].

Wauquier et al have noted that T lymphocyte levels in survivors are roughly five times greater than those found in deceased patients. Consequently, an effective, active and quick lymphocyte mediated immune response might be enough to contain the disease from progressing [88].

The signaling pathways induced by the EBOV which cause lymphocyte apoptosis are related mainly to the TRAIL (TNF-related apoptosis-inducing ligand) and Fas (CD95) pathways, with the latter being the most common of the two [127,128]. The first pathway is activated by TNF (mainly TNF-α), since its levels increase during the cytokine storm and can therefore be related to this phenomenon [129]. The second pathway is activated by its ligand (FASL), which is considered a cellular death protein, since it leads the cell towards apoptosis due to the caspase pathway [67]. Another exacerbating factor for leucocyte apoptosis is the excessive production of nitric oxide due

to the viral invasion of macrophages and dendritic cells [130]. This lymphapoptosis puts the patient in an immunodeficient state, making him or her considerably more susceptible to virtually any other kind of infection [131,132].

An elevated mortality rate has been seen in patients with a suppressed humoral response, which is associated to the previously discussed lymphopenia [133,134] (Figure 1).
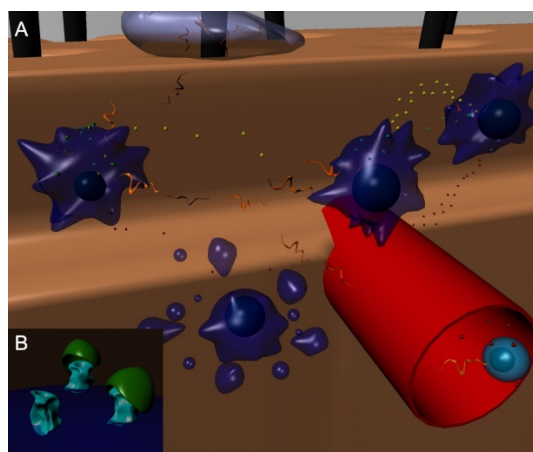

Figure 1: Cytokine storm provoked by the Ebola Virus. A) Dendritic Cells (DC), the right cell represents a healthy DC is secreting great amounts of different cytokines such as IL, IFN and TNF in response to the presence of EBOV, the left dendritic cell is being affected by the presence of the virus and decreases its expression of IFN and some ILs previously described, as a consequence of the Ebola Infection. Observe the multiple interactions between cells and the secreted virus glycoproteins (GP) to the environment. GP can affect endothelium cells as well as other cells. Furthermore, this interactions cause death cell pathway activation in Leucocytes. B) Steric Shielding produced by EBOV. Observe the MHC receptors being blocked by GP.

Clotting Abnormalities

Massive hemorrhages throughout the body are one of the cardinal points of EBOV infection [135]. These coagulation defects present as ecchymosis, petechiae and uncontrollable hemorrhages [45]. These hemostatic defects can lead to Disseminated Intravascular Coagulation (DIC), a potentially fatal condition distinguished by the formation of intravascular thrombi and an uncontrollable activation of the coagulation cascade [136-138].

Tissue factor (one of the coagulation cascade's initiators) is overexpressed in monocytes and macrophages, probably due to the cytokine storm [139]. Although part of this factor is produced in vascular endothelium, this amount would not explain the widespread activation of the coagulation cascade seen in EBOV infection. The expression of tissue factor in monocytes and macrophages can cause DIC, which will result in the formation of several fibrin meshes in affected organs Figure 2 [140].
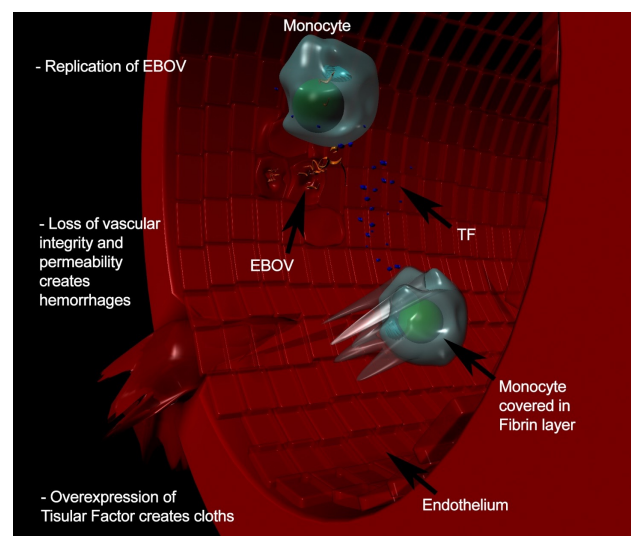

Figure 2: The image represents a vascular endothelium. It is important to highlight the release of virus to par-shooting of the tissue factor released from monocytes and endothelial cells. Note the loss of vascular integrity causing bleeding during the illness. TF: Tissue Factor; EBOV: Ebola Virus.
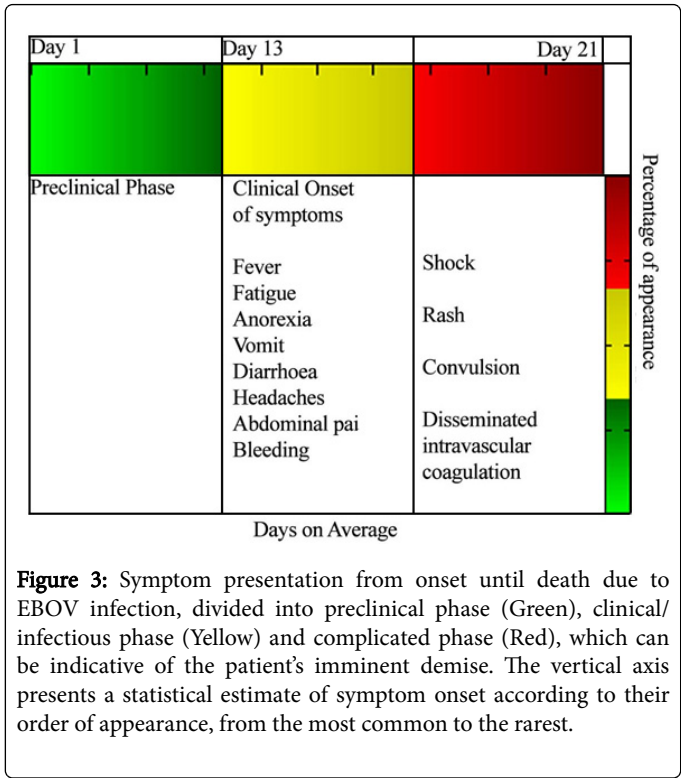
Geisbert et al found fibrin around macrophages infected by EBOV in the first four days following exposure to the pathogen [139]. This is relevant due to the association that fibrin has with multiple organic failure [141].

Clinical Picture

Filovirus infections in humans have an abrupt onset [142]. They are distinguished by the appearance of fever, myalgias, headaches, and gastrointestinal symptoms such as nausea, vomit and diarrhea, similar to the initial stages of infection by influenza [34]. Several patients present a maculopapular eruption roughly 5-7 days after the onset of symptoms [143]. Mortality is associated with an increase in viremia along the course of the infection. The disease can eventually lead to shock, seizures and disseminated intravascular coagulation [144,145].

A study conducted in the Democratic Republic of the Congo analyzed the frequency of several symptoms in patients infected with ZEBOV. The most common symptoms were fever (92%), intense fatigue (71%), diarrhea, nausea or vomit (68%), abdominal pain (47%), headaches and myalgia (45%), anorexia (39%), dysphagia (26%) and conjunctivitis (16%) [146].

A more recent study showed that the most frequent symptoms are fever (87.1%), fatigue (76.4%), anorexia (64.5%), vomit (67.6%), diarrhea (65.6%), headache (53.4%), abdominal pain (44.3%) and apparently unexplainable hemorrhages (18%) [147] Figure 3.

Figure 3: Symptom presentation from onset until death due to EBOV infection, divided into preclinical phase (Green), clinical/infectious phase (Yellow) and complicated phase (Red), which can be indicative of the patient's imminent demise. The vertical axis presents a statistical estimate of symptom onset according to their order of appearance, from the most common to the rarest.

EBOV generally has a 2-21 day incubation period, with an average of 12.7 days [148-150]. Beginning at symptom onset, patients acquire the ability to infect others in the ways previously described [148]. The latency period lasts approximately 10 days [33]. The average amount of time between symptom onset and death is 10 days [9,151]. More severe cases show a much faster symptomatic progression, leading to death 6-16 days after symptom onset [151]. Only 19% of patients have shown bleeds without an apparent cause in the current outbreak [147,152].

Some researchers have aimed to aid the diagnosis of EBOV infection using laboratory studies, since the clinical picture can be quite similar to other hemorrhagic fevers. The most accurate study so far has been quantitative RT-PCR, which gives an infected patient's viral load [153,154]. Patients with a viral load exceeding 10 million copies have an approximate mortality rate of 94%. On the other hand, patients with a viral load beneath 100,000 copies tend to have a high survival rate. Furthermore, a study conducted in Sierra Leone during the 2014 outbreak showed that mortality is more closely linked to a patient's viral load than his o hers amount of time exposed to the virus [154].

Treatment and Outcome

Multiple supportive care therapies have been implemented in infected patients. For instance, some hospitals in Sierra Leone and Liberia have administered abundant intravenous fluids along with antibiotics such as ceftriaxone [153,155]. The ZMapp vaccine, which was developed using monoclonal antibodies aimed to halt the disease's progression, was tested during the 2014 outbreak [156].

A patient can be considered cleared of the disease after the diseased period (approximately 14 weeks), followed by 9 weeks with no evident viremia. Ebola survivors are not infectious and it is believed that they develop resistance to the disease [157].

Recently, Ebola ca Suffit or "Ebola this is enough" cluster randomized phase 3 trial, a new Ebola vaccine that is leaving other vaccine candidates far off, claiming in a paper published by The Lancet [158], that the phase III trial has very promising results, using a recombinant, replication competent vesicular stomatitis virus, they were able to express a surface glycoprotein of ZEVOB and a nobel way of identifying high risk subjects and their contacts called Ring Vaccination, defined as vaccination of a cluster of individuals at high risk infection. The team identified all the subjects that were in close contact with a confirmed case of ZEBOV in Guinea, as well as the contacts of those contacts, being identified as clusters. Began on March 23, 2015 and consisted in administration of one dose of 2×10^7 plaque forming units of the rVSV-ZEBOV vaccine to candidates as an intramuscular injection in the deltoid muscle to adult contacts and contacts of contacts of patients with confirmed EBOV infection, then they were subjected to observation for 30 minutes for signs of immediate adverse effects, then again on days 3,14,21,42,63 and 84 post vaccination, any clinical manifestation resulting in EBOV infection would be then confirmed by detection of EBOV RNA by reverse transcriptase PCR.

Out of ninety clusters that included 7700 people were randomized to vaccinate immediately or delay vaccination by 3 weeks, depending on the risk of infection, after 10 days there was not a single case of ZEBOV infection in the immediate vaccination group with a 100% vaccine efficacy, however the delayed vaccination group presented 16 cases of infection. There was also 1 case of febrile illness linked to vaccination but the patient recovered without any further complications [158,159].

Conclusion

A lot of dedicated research has taken place in the fields of virology and medicine to try and understand the Ebola virus pathophysiology and transmission mechanisms. Thousands of people have died in recent outbreaks, several of which were part of humanitarian forces from international organizations trying to protect the health and wellbeing of others. This review could not have been written without their brave efforts. A vaccine is on its way and effective treatment still seem to be far away, however, the scientific community is working relentlessly to try and put a halt to this fulminant disease.

Acknowledgments

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