

Ebola Virus Disease, Management, and Prevention

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Abstract: Ebola virus was first discovered in 1976, WHO reports 24 outbreaks, 28,633 cases and 11,315 deaths in the recent outbreak. Human to- human transmission of Ebola virus (EBOV) not been reported, the spread is due to direct contact with infected wild animal, fruit bat or contact with blood, body fluids of the infected person. Natural reservoir for Ebola virus yet to be confirmed, bats are likely reservoir species. Pathogenesis process occurs in monocyte-macrophages, and leads to disseminated intravascular coagulation (DIC), precedes endothelial damage, EBOV proteins evade the immune system resulting in the body cell's ability to produce and respond to interferon proteins. Early symptoms of Ebola virus disease (EVD) may be similar to other diseases including malaria and dengue fever. In some cases internal and external bleeding may occur. WHO approved rapid antigen test which gives results in 15 minutes. The test is reliable to confirm Ebola in 92 % of those affected and rule out in 85 % of those not affected. Treatment is primarily supportive in nature, rehydration and symptomatic treatment improves survival. Death risk those infected varies between 25 percent to 90 percent. Ebola can stay in the eyes, breast, testicles, and sexual transmission has been suggested. EVD have heavy economic impact on the affected countries.

Keywords: Ebolavirus disease, Ebola hemorrhagic fever, mortality, Diagnosis, and management

I. Introduction

Ebola virus disease (EVD), also Ebola hemorrhagic fever, or EHF or simply Ebola is viral hemorrhagic fever of humans and other primates caused by ebolaviruses [1]. Disease was first recognized in 1976 in two simultaneous outbreaks, one in Nzara, and other in Yambuku, a village near Ebola River from which the disease carries its name [2]. Between 1976 and 2013, the World Health Organization reports a total of 24 outbreaks involving 1,716 cases [1]. The largest outbreak is the recent epidemic in West Africa, which affected Liberia and Sierra Leone [3]. As of December 2015, this outbreak has 28,638 cases resulting in 11,315 deaths [4]. In the U.S. health officials confirmed one death due to Ebola in October, 2015, patient had recently returned from Liberia [5]. The virus spreads by direct contact with body fluids, such as blood, of an infected human or other animals [1]. Transmission through air between primates, including humans has not been documented in either laboratory or natural conditions [6]. Semen or breast milk of a person after recovery from EVD may carry the virus for several weeks to months [1]. EVD may resemble other diseases such as malaria, cholera, typhoid fever, meningitis and other viral hemorrhagic fevers [1]. Clinical symptoms start between two days and three weeks after contracting the virus, with fever, sore throat, muscular pain, and headaches, vomiting, diarrhea and rash follow, along with decreased function of liver and kidneys. At this time some people begin to bleed both internally and externally [1]. Disease has high mortality between 25 and 90 percent, an average about 50 percent [1]. Diagnosis is by detection of viral RNA, viral antibodies or the virus itself to confirm the diagnosis [1]. No specific treatment or vaccine for virus is available, supportive efforts, however improve outcomes. The paper reviews the current literature, clinical presentation, prevention and economic impact of EVD on the affected country.

II. Etiology of EVD

Ebolaviruses contain single-stranded non-infectious RNA genomes [7]. Ebolavirus genomes contain seven genes including 3'-UTR-NP-VP30-VP40-GP-VP30-VP24-L-S-UTR [8]. The genomes of the five different ebolaviruses (BD0V, EB0V, RESTV, SUD and TAFV) differ in sequence and the number and location of gene overlaps. As with all filoviruses, ebolavirus virions are filamentous particles that may appear in the shape of a shepherd's crook, of a "U" or a "6" and they may be coiled, toroid or branched [8]. In general, ebolavirions are 80 nanometers (nm) in width and may be as long as 14,000 nm [9].

Filoviruses the name of the virus family comes from their characteristic threadlike (*filo*, Latin for "filament"), morphology of this has made their recognition in tissues or clinical sample [10]. Filoviruses are commonly encountered and their natural history is only now being understood. Because the serious human disease they cause and our lack of predictive information about them. The identification of Marburg virus in

1967 was the first of only a handful of independent isolation of Marburg virus or related Ebola virus from humans [11].

In 1967, African green monkeys were brought from Uganda to Europe for use in vaccine production and biological research. They were infected with a “new” virus that resulted in deaths among the monkeys and transmission to humans. Seven deaths occurred among 25 primary and 6 secondary human cases [12]. After 3 other isolated human cases with limited transmission, a major epidemic occurred in Angola with 252 cases with 90% case fatality rate. The case fatality rate was surprisingly high because in the former epidemics, only about one third of cases died. It is not known why this virus appeared to be so virulent but fell within the pathogenetic group of major clade of Marburg viruses, although the virulence in macaques appears to be higher than other strains. The second large Marburg virus epidemic occurred over a prolonged period from 1998 to 2000 [13]. This outbreak was epidemiologically linked to an underground gold mine and had multiple introductions of Marburg viruses of different pathogenetic lineages. This provided a major opportunity to implicate bats as reservoirs and indeed reverse transcriptase-polymerase chain reaction (RT-PCR) products and antibody were found in several bats and represented slightly different genotypes [10].

Ebola virus was first recognized in 1976, when two unrelated epidemics occurred in northern Zaire and 850 km away in southern Sudan; 88% of the patients in 318 recognized cases died in the former, and 35% of 284 in the later [14]. Disease recurred in the same area in 1979 [15]. Ebola hemorrhagic was not recognized for almost two decades. Then, in 1995 and 1996 an additional Ebola subtype (Cote d’Ivoire) was isolated from human patients [16], three separate Zaire subtype epidemics were recognized in Gabon [17], and major epidemic (315 cases, 81% case fatality rate) from the Zaire subtype occurred in Kikwit, Zaire [18]. Notably one Gabon patient made his way from Libreville, where he fell ill, to a modern hospital in South Africa [19]. Despite the fact that his infection was not recognized as Ebola, he transmitted the disease to only a single nurse. This secondary infection was unfortunately fatal, but the entire episode illustrated the low risk in a modern hospital setting. More recently, smoldering outbreaks of Sudan and Zaire virus subtypes have occurred in Uganda [7], and Congo [20].

In 1989 to 1991, another subtype was discovered in Reston, Virginia, among dying cynomolgus monkeys imported from Manila, Philippines [21]. This virus proved to be highly virulent for macaques, but the four animal caretakers who were infected suffered no overt disease. Other episodes occurred in Italy in 1992 and in the United States in 1996 [22]. All these were traced to the facility of a single exporter, but ultimate source of the virus has never been ascertained, although Mindanao was the origin of the monkeys taken for conditioning and resale [23]. In 2009, an outbreak of Reston Ebola virus was discovered in pigs in the Philippines, and the antibody evidence of human infection was also found [18].

III. Transmission

Ebola spreads only by direct contact with blood or body fluids of a person who has developed symptoms of disease [24]. Body fluids that may contain Ebola viruses include saliva, mucous, vomit, feces, sweat, tears, breastmilk, urine and semen [24]. Entry points for the virus include the nose, mouth, eyes, open wounds, cuts and abrasions [25]. Ebola may spread through large droplets, however, this is believed to occur only when a person is very sick [26]. This contamination can happen if a person is splashed with droplets [26]. Contaminated needles and syringes may also transmit the infection [27]. The virus is able to survive on objects for a few hours in a dried state, and can survive for a few days within body fluids outside of a person [25].

Ebola virus may be able to persist for more than 3 months in semen after recovery, which could lead to infection through sexual intercourse [24]. Ebola may also occur in the breast milk of women after recovery, and it is not known when it is safe to breastfeed again [28]. Health-care workers treating people with Ebola are at great risk of infection [27]. The risk increases when they do not have appropriate clothing such as masks, gowns, gloves and eye protection, do not wear properly, or handle contaminated clothing incorrectly [27]. Dead bodies remain infectious; thus, people handling remains in practices such as traditional burial rituals or more modern processes such as embalming are at risk [29]. The potential for widespread infections in countries with medical systems capable of observing correct medical isolation procedures is considered low [29].

Human to-human transmission of EBOV through air has not been reported to occur during outbreaks [6], and airborne transmission has not been demonstrated in very strict laboratory conditions, and then only from pigs to primates, but not from primates to primates [30]. The apparent lack of airborne transmission among humans is believed to be due to low levels of virus in the lungs and other parts of respiratory systems of primates, insufficient to cause new infection [31]. Spread of EBOV by water or food other than bush meat, has not been observed [27]. No spread by mosquitos or other insects has been reported [27].

Although it is not entirely clear how Ebola initially spreads from animals to humans, the spread is believed to involve direct contact with an infected wild animal or fruit bat [27]. Besides bats, other wild animals sometimes infected with EBOV include several monkey species, chimpanzees, gorillas, baboons and duikers [32]. Animals become infected when they eat fruit partially eaten by bats carrying the virus [33]. Evidence

indicates that both dogs and pigs can also be infected with EBOV[34].The natural reservoir for Ebola yet to be confirmed, however bats are considered to be the most likely candidate species[35].

IV. Pathophysiology

Filovirus disease has findings that are similar in human patients and nonhuman primate models. The viremia persists throughout the acute period, and its disappearance coincides with clinical improvement and usually appearance of antibodies in the blood [36].Similar to other filoviruses,EBOV replicates very efficiently in many cells, producing large amounts of virus in monocytes, macrophages, dendritic cells and other cells including liver cells, fibroblasts, and adrenal gland cells[37].EBOV is thought to infect humans through contact with mucous membranes or through skin breaks[30].Once infected, endothelial cells(cells lining the inside of blood vessels),liver cells, and several types of immune cells such as macrophages ,monocytes, and dendritic cells are the main targets of infection[30].Following infection with virus, the immune cells carry the virus to nearby lymph nodes where further reproduction of virus takes place[30].From there, the virus can enter the bloodstream and lymphatic system and spread throughout the body[30].Macrophages are the first cells infected with the virus, and this infection results in programmed cell death[9].Other types of white cells, such as lymphocytes, also undergo programmed cell death leading to an abnormally low concentration of lymphocytes in the blood[30]This contributes to the weakened immune response seen in those infected with EBOV[30]. Endothelial cells may be infected within three days after exposure to the virus [9].The breakdown of endothelial cells leading to blood vessel injury can be attributed to EBOV glycoproteins. This damage occurs due to the synthesis of Ebola virus glycoprotein (GP), which reduces the availability of specific integrin's responsible for cell adhesion to the intracellular structure and causes liver damage, leading to improper clotting. The widespread bleeding that occurs in affected people causes swelling and shock due to loss of blood volume[38].The dysfunction in bleeding and clotting commonly seen in EVD has been attributed to increased activation of the extrinsic pathway of the coagulation cascade due to the excessive tissue factor production by macrophages[39]. Important morphologic lesions include focal necrosis in many organs, particularly the liver, where Councilman bodies are present, and the lymphoid organs, where prominent follicular necrosis occurs [14].Necrotic lesions are found in conjunction with antigen and viral particles in endothelial mononuclear, and parenchymal cells of virtually all organs. In addition to the morphologic basis for the multi-organ functional defects, cytokines are extensively activated in sick humans [40].A major cause of the pathogenesis in experimental monkey infections is activation of tissue factor which occurs first in monocyte-macrophages, and leads to disseminated intravascular coagulation (DIC),which precedes direct viral endothelial damage[41].

Avoidance of immune system

Filoviral infection also interferes with proper functioning of the innate immune system [42].EBOV proteins blunt the immune system's response to viral infections by interfering with the cell's ability to produce and respond to interferon proteins such as interferon-alpha, interferon-beta, and interferon gamma [43].The VP24 and VP 35 structural proteins of EBOV play a key role in this interference. When a cell is infected with EBOV,receptors located in the cell's cytosol(such as RIG-1 and MDA5) or outside of the cytosol (such as Toll-like receptor 3(TLR3),TLR7,TLR8 and TLR9),recognize infectious molecules associated with the virus[42].On TLR activation, proteins including interferon regulatory factor 3 and interferon regulatory factor 7 trigger a signaling cascade that leads to the expression of type 1 interferons[42].The type 1 interferons are then released and bind to the IFNAR 1 and IFNAR2 receptors expressed on the surface of a neighboring cell[42].Once interferon has bound to its receptors on the neighboring cell, the signaling proteins STAT1 and STAT2 are activated and move to the cell's nucleus[42].This triggers the expression of interferon-simulated genes, which code for proteins by preventing the STAT1 signaling protein in the neighboring cell from entering the nucleus[43].The VP35 protein directly inhibits the production of interferon-beta[44].By inhibiting these immune responses,EBOV may quickly spread throughout the body[9].

V. Clinical Presentation

The incubation period between exposure and development of symptoms is between 2- to 21days,and usually between 4 to 10 days[1,45,39].Symptoms usually begin with a sudden influenza-like stage characterized by feeling tired,fever, weakness, decreasedappetite, muscularpain, joint pain, headache, and sore throat[1].The fever is usually higher than 38.3°C[46].This often followed by vomiting, diarrhea and abdominal pain[47].Next,shortness of breath and chest pain may occur, along with swelling, headache and confusion[47].In about half of the cases, the skin may develop a maculopapular rash, a flat red area covered with small bumps,5 to 7 days after symptoms begin[39].

Internal and external bleeding

In some cases internal and external bleeding may occur[1].This typically begins five to seven days after the first symptoms[48].All infected people show some decreased blood clotting[46].Bleeding from mucous membranes or from sites of needle punctures has been reported in 40 to 50 percent of cases[49].This may cause vomiting blood, coughing up of blood, or blood in stool[50].Bleed into the skin may create petechiae, purpura, ecchymoses or hematomas(especially around needle injection sites)[51].Bleeding into whites of eyes may also occur. Heavy bleeding is uncommon, if it occurs, it is usually located within the gastrointestinal tract [46].Recovery may begin between 7 and 14 days after first symptoms[48].Death if occurs, follows typically 6 to 16 days from first symptoms and is often due to low blood pressure from fluid loss[52].In general bleeding often indicates a worse outcome, and blood loss result in death[[53].People are often in a coma state near the end of life[47].Those who survive often have ongoing muscular and joint pain, liver inflammation, decreased hearing, and may have continued feeling of tiredness, continued weakness, decreased appetite, and difficulty to returning to pre-illness weight [45].Problem with vision may develop[54].Additionally they develop antibodies against Ebola that last at least 10 years, but it is not clear if they are immune to repeated infections[25].

VI. Diagnosis

Travel to rural sub-Saharan Africa (and now perhaps the Philippines) or exposure to nonhuman primates is a historical clue [55].When EVD is suspected in a person, his or her travel and work history, along with exposure to wildlife, are important factors to consider with respect to further diagnostic efforts[56].Possible non-specific laboratory indicators of EVD include a low platelet count, an initially decreased white blood cell count followed by an increased white blood cell count, elevated levels of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase(AST) and abnormalities in blood clotting often consistent with disseminated intravascular coagulation(DIC) such as prolonged prothrombin time, partial thromboplastin time and bleeding time[56].Filoviruses, such as EBOV may be identified in cell culture, examined with electron microscope[57].Isolating the virus by cell culture, detecting the viral RNA by polymerase chain reaction(PCR)[39], and detecting proteins by enzyme-linked immunosorbent assay(ELISA) are the methods used in the early stage, and detecting the antibodies against the virus in the later stages of disease and in those who recover[58].*In 2015 a rapid antigen test which gives results in 15 minutes was approved by WHO. It is reliable to confirm Ebola in 92 % of those affected and rule it out in 85% of those not affected [59].*

Early symptoms of EVD may be similar to those of other diseases common in Africa, including malaria and dengue fever [51].The symptoms are also similar to those of other viral hemorrhagic fevers such as Marburg virus disease[60].Differential diagnosis is extensive and requires consideration of many other infectious diseases such as typhoid fever, shigellosis, rickettsia diseases, cholera, sepsis, borreliosis, EHEC, enteritis, leptospirosis, scrub typhus, plague, Q fever, candidiasis, histoplasmosis, trypanosomiasis, visceral leishmaniasis, measles, and viral hepatitis among others[61].Non-infectious diseases with similar symptoms as EVD include acute promyelocytic leukemia, hemolytic uremic syndrome, snake envenomation, clotting factor deficiencies/platelet disorders, thrombotic thrombocytopenic purpura, hereditary hemorrhagic telangiectasia, Kawasaki disease, and warfarin poisoning[62].

VII. Management.

No specific treatment is currently approved [63].Treatment is primarily supportive in nature[64].Early supportive care with rehydration and symptomatic treatment improves survival[1].Rehydration may be via the oral or by intravenous route. These measures may include management of pain, nausea, fever and anxiety[64].The WHO recommends avoiding the use of aspirin or ibuprofen for pain due to the bleeding risk associated with use of these drugs[65].Other regulators of coagulation have been tried including heparin in an effort to prevent disseminated intravascular coagulation(DIC) and clotting factors to decrease bleeding[64].Intensive care is often useful in the developed world [49].This may include maintaining blood volume and electrolytes (salts) balance as well as treating any bacterial infections that may develop [49].Dialysis may be needed for kidney failure, and extracorporeal membrane oxygenation may be used for lung dysfunction [49].The WHO guidelines for care at home include using towels soaked in bleach solutions when moving infected people or bodies and applying bleach on stains. It is also recommended that the caregivers wash hands with bleach solutions and cover their mouth and nose with a cloth [66].In September 2014, an Ebola vaccine was used after exposure to Ebola and person appears to have developed immunity without getting sick[67].In July 2015 early results of a trial of the vaccine VSV-EBOV showed effectiveness[68].

VIII. Prognosis and Prevention

EVD has high risk of death in those infected which varies between 25 percent to 90 percent of those infected [1].As of September 2014, the average risk of death among infected is 50 percent[1].The highest risk of death was 90 percent in 2002-2003 Republic of Congo outbreak[69].Death, if it occurs follows typically six to

sixteen days after symptoms appear and is often due to low blood pressure from fluid loss[50]. Early supportive care to prevent dehydration may reduce the risk of death[70]. If an infected person survives, recovery may be quick and complete. Prolonged cases are often complicated by occurrence of long-term problems, such as inflammation of the testicles, joint pains, muscular pain, skin peeling, or hair loss [39]. Eye symptoms, such as light sensitivity, excess tearing, and vision loss have been described[71]. Ebola can stay in some body parts like eyes, breast, and testicles[72,24]. Sexual transmission after recovery has been suggested. If sexual transmission occurs following recovery it is believed to be a rare event. One case a condition similar to meningitis has been reported many months after recovery as of October 2015[73-75].

Prevention

Prevention of epidemics rests on early recognition of initial cases and prompt institution of barrier nursing[39]. Increased clinical awareness should lead to the barrier nursing, which can be done with means appropriate to the African health care setting[76]. Fatal cases can be recognized readily by immunohistochemical staining of postmortem skin samples, obviating the need for cold preservation of samples and providing a safe and inexpensive diagnostic modality in these high-mortality diseases[77]. In 2014 began recommending that medical personnel receive training on the proper suit-up and removal of personal protective equipment (PPE)[78]. In Sierra Leone, the typical training period for the use of such safety equipment lasts approximately 12 days [79]. CDC recommends monitoring for symptoms of Ebola disease for those both at “low risk” and at higher risk[80]. In laboratories diagnostic testing is carried out, biosafety level (BSL)-4 equivalent containment is required[81]. Laboratory researchers must be trained in BSL-4 practices and wear proper PPE[81].

IX. Economic Impact

EVD have high economic burden on the affected countries. Ebola outbreak in west African nations, general per capita income is expected to fall by US\$18.00 per year, and Gross Domestic Product (GDP) fall from 4.5 percent to 3.5 percent[82]. United Nations Development Group (UNDG) estimated that west Africa may lose an average of at least US\$3.6 billion per year between 2014 to 2017, due to decrease in trade, closing of borders, flight cancellations, reduced Foreign Direct Investment (FDI), and tourism activity [83]. World Health Organization (WHO) reported that poverty rate has risen by at least by 0.5 percent, and people living below poverty line could increase by up to 2.0 percent[84]. One research study reported that women are typically self-employed and percentage of women out of work affected dearly. Agriculture households in 2014 harvest were smaller than the previous year. These low economic effects were not restricted to the areas that have been directly impacted by Ebola, underlining the need to provide broad agriculture support across the country [85].

X. Conclusion

Ebola virus disease (EBV) or Ebola hemorrhagic fever (EHF) is caused by ebolaviruses. Disease has high mortality and no specific treatment or vaccine. Diagnosis by detection of viral RNA, viral antibodies or virus itself. Treatment is mainly supportive in nature.

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