

Epidemiology and pathogenesis of Ebola viruses

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The family *Filoviridae* consists of three genera, the Ebolaviruses, Marburgviruses, and the recently described Cuevaviruses. The two first of them belong among the most virulent viruses. The Ebola viruses, respectively Zaire species of this genera is the causative agent of the biggest ebola outbreak, namely West Africa Ebola Outbreak, which started in 2014, and in which the case-mortality rate has been reported to be at about 50 percent, with the number of total cases exceeding twenty-four thousands [1]. In comparison with earlier Ebola outbreaks mortality have been higher (80 - 90 percent), but number of cases was a thousand times lower. In this study will be presented epidemiology and pathogenesis of Ebola virus disease including new findings resulting from the studies linked with 2014 Ebola Outbreak in West Africa. The EVD epidemiology, pathogenesis, and clinical characterization will be discussed in this study.

Keywords: Ebola virus, Ebola virus diseases, hemorrhagic fever, West Africa Ebola Outbreak

1. Basically about Ebola viruses

The Ebola viruses (EBOV) are enveloped, non-segmented, negative-sense, single-stranded RNA viruses, with size of genome approximately 19 kbp [2]. The virion is pleomorphic, producing 'U'-shaped, '6'-shaped, or circular forms [3]. The EBOV may cause a disease in humans as well as in non-human primates, called Ebola virus disease (EVD). EBOV are firstly described in 1976, since than five species of the EBOV were described since. Four of them: Sudan virus (SUDV), Ebola virus (EBOV, known as Zaire), Taï Forest virus (TAFV), and Bundibugyo virus (BDBV) cause acute and lethal disease in human population [4, 5]. The fifth, Reston virus (RESTV), differs from each other, it has been caused disease only in monkeys, chimpanzees, and gorillas and it is apparently maintained in an animal reservoir in the Philippines and has not been found in Africa [6, 7]. Since 1976, more than twenty outbreaks of EVD have been reported in Africa [8]. The current outbreak,

West Africa Ebola Outbreak 2014 (WAE0), first reported by the World Health Organization (WHO) on 22 March 2014, was caused by ZEBOV and is responsible for more than ten thousands death [9]. In addition to the three most affected countries in sub-Saharan Africa (Guinea, Liberia and Sierra Leone), EBOV cases have been reported in the Great Britain, the United States and Spain [1, 10]. The behavior of WAE0 was so alarming, that some countries decided to implement special measures for air plane transport of passengers from affected countries [11].

2. Ebola virus disease

EBOV cause severe hemorrhagic fever with high percentage of fatal outcome in humans, and several species of non-human primates (NHPs) [12]. Human Ebola outbreaks usually occur abruptly from a vaguely defined source, with subsequent rapid spread from person to person [13]. In the past, EBOV were classified as „hemorrhagic fever viruses“, based on the

clinical manifestations, which include coagulation defects, bleeding, and shock [14, 15]. But this term is no longer used because not all of Ebola patients developed significant hemorrhage symptoms, which usually occurs only in the terminal phase of fatal illness [16].

3. Epidemiology of EVD

Two main modes of transmission into human populations have been suggested: either direct contact to a reservoir or contact to other wildlife that also contracts EBOV from the reservoir [17]. Epidemiologic observations showed that chimpanzees were the source of one human case in two recently described outbreaks (Côte d'Ivoire in 1994 and Gabon in 1996) [13]. Transmission of EBOV in human population happens by direct contact with infected blood, or other bodily fluids (saliva, sweat, semen, milk), and tissues from dead or living infected persons [18]. Transmission via inanimate objects contaminated with infected bodily fluids is possible, the principal mode of transmission in human outbreaks is human-to-human transmission through direct contact with a symptomatic or dead EVD case or with contaminated surfaces and materials (bedding, clothing) [19, 20]. The risk for transmission is lower in the early stage of human disease (prodromal phase), but viral loads in blood and secretions rapidly increase during the course of illness, with the highest levels of virus shedding observed late in the course of illness of severely ill patients [21, 22]. Burial ceremonies and handling of dead bodies play an important role in transmission [20]. Amplified transmission occurs in hospitals (approximately one quarter of cases occurring among health care workers) [6].

Human, non-human primates and some other mammalian can be infected by EBOV and regarded as host, but reservoir of Ebola viruses was for a long period hidden. An intensive efforts were expended to identify the natural reservoir [18]. Previously some researchers suggested, rodents and bats could play role as reservoir animals of EBOV [23, 24]. First report about EBOV infected bats was verified by detection of antibodies and viral RNA in three bats species

[25, 26]. What proved, that bats are involved in circulation of EBOV in nature [27]. Transmission of EBOV to humans in sub-Saharan Africa thought the contact with dead or living infected animals (non-human primates, antelopes and bats), although some studies traced cases back to the skinning and butchering of carcasses [28, 29]. Hunting and butchering of chimpanzee and fruit bats has been identified in previous outbreaks as a potential source of infection [3, 7]. Leroy et al. presented, the human outbreaks consisted of multiple simultaneous epidemics caused by different viral strains, and each epidemic resulted from the handling of a distinct gorilla, chimpanzee, or duiker carcass [30]. Due to this facts surveillance of wildlife health and monitoring of their mortality may help to predict and prevent next Ebola outbreaks.

4. Clinical characterization and pathogenesis of EVD

The incubation period of EVD ranges between seven to ten days [31], but can be shorter (two days) or longer (21 days) [7]. Virus presence in blood is usually detectable one day before clinical symptoms appear, using polymerase-chain-reaction-based methods, increasing amounts of virus in the bloodstream are accompanying events of the fatal illness [32]. Case fatality rates have varied from 44 to 90 percent, depending on the strain of EBOV, the level of medical care, and public awareness, etc. [33]. Typically clinical symptoms of EVD are sudden onset of fever, accompanied by flu-like symptoms, such as headache, malaise, myalgia, eventually vomiting, and diarrhea [20]. Only in 30–50 percent of EVD patients developed hemorrhagic symptoms [34]. Severe cases of disease are characterized by hepatic damage, renal failure together with multi-organ dysfunction, and central nervous system complication [7]. Mortality is caused by multi-organ failure and severe bleeding sites [7, 35]. During the terminal phase of illness, infected patients bleeding massively from the gastrointestinal tract affected by disseminated intravascular coagulation are relatively rare [7, 15]. Conversely, patients who survive infection show a decrease in amounts of circulating virus and clinical improvement

around day 7–10, what is usually linked with the occurrence of EBOV-specific antibodies [36]. Non-fatal or asymptomatic cases tend to be associated with a specific IgM and IgG responses and early and strong inflammatory response, including interleukin β , interleukin 6, and tumor necrosis factor α [7]. EBOV infected animals showed renal lesions with disseminated microvascular thrombosis evident in glomerular capillaries leading to acute kidney injury due to hypoperfusion [37]. Minimal or mild changes with no clinical significance were observed on lungs as a respiratory failure is not a common feature of EBOV [38]. Lesions on livers of infected macaques developed hepatic necrosis with mild to moderate inflammation, moreover elevation of hepatocellular and pancreatic enzymes are frequently presented [39, 40].

The pathogenesis of the disease is still not completely known. EBOV can enter the host body mostly via mucosal surfaces, or injuries in the skin [41]. Also infection through the intact skin cannot be excluded, although it is

considered unlikely. Aerosol infection (RESTV) has been demonstrated in non-human primates under experimental conditions in dispersion chambers [42, 43]. EBOV infection is characterized by immune suppression and a systemic inflammatory response, which could cause damage of the vascular, and immune systems, that can lead to multiorgan failure and shock [7]. Geisbert et al. presented study in non-human primates and showed that EBOV replicates in monocytes, macrophages, and dendritic cells; however, in situ hybridization and electron microscopy have also shown the presence of virus in endothelial cells, fibroblasts, hepatocytes, and adrenal cells [44]. Del Rio et al. demonstrated, the EBOV disseminates to the lymph nodes, liver, and spleen [6].

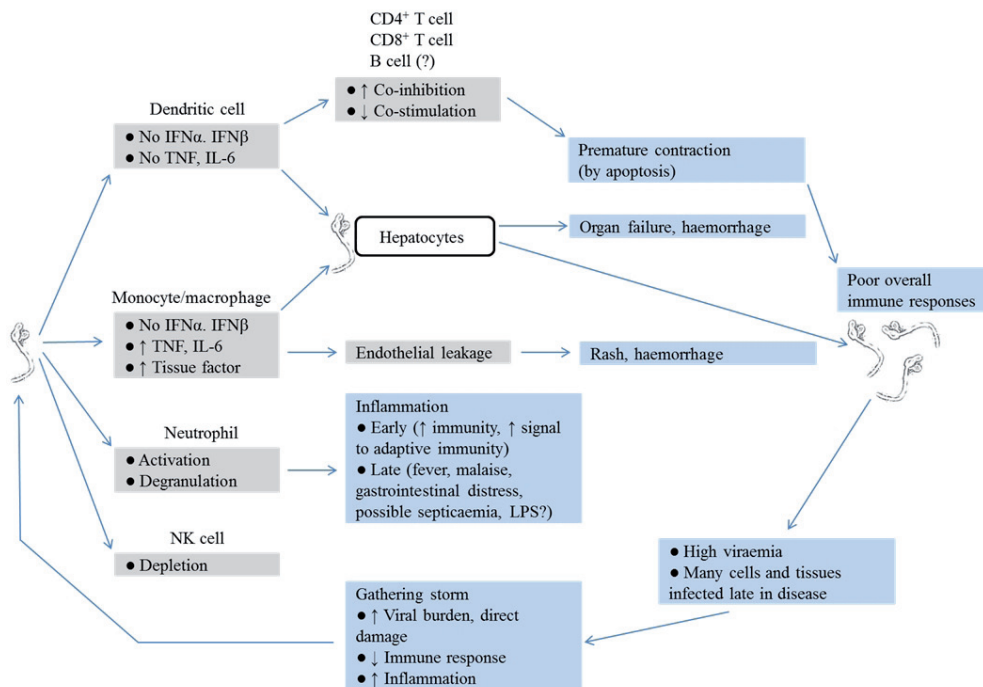


Figure 1: Overview of Ebola virus pathogenesis

4. Conclusions

The understanding of EBOV pathogenesis is crucial for the development of efficacious treatments and vaccines. Targeted therapy and vaccination are an immediate and highest priority. The danger, hidden in high virulent and infectious EBOV, breakdown of public health and preventive measures, and create significant challenges ahead. Resolving all of issues connected with EBOV will require long term and collaboration of scientific community with multinational organizations.

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Conflicts of Interest

The authors declare they have no potential conflicts of interests concerning drugs, products, services or another research outputs in this study. The Editorial Board declares that the manuscript met the ICMJE „uniform requirements“ for biomedical papers.

References

- Kuhn, J.H., et al., Filovirus RefSeq Entries: Evaluation and Selection of Filovirus Type Variants, Type Sequences, and Names. *Viruses-Basel*, 2014. 6(9): p. 3663-3682.
- WHO. Current Situation. 2015; Available from: <http://apps.who.int/ebola/en/current-situation>.
- Bray, M. and F.A. Murphy, Filovirus research: Knowledge expands to meet a growing threat. *Journal of Infectious Diseases*, 2007. 196: p. S438-S443.
- Reid, S.P., et al., Ebola virus VP24 binds karyopherin alpha 1 and blocks STAT1 nuclear accumulation. *Journal of Virology*, 2006. 80(11): p. 5156-5167.
- Muyembe-Tamfum, J.J., et al., Ebola virus outbreaks in Africa: Past and present. *Onderstepoort Journal of Veterinary Research*, 2012. 79(2): p. 06-13.
- Del Rio, C., et al., Ebola hemorrhagic Fever in 2014: the tale of an evolving epidemic. *Annals of internal medicine*, 2014. 161(10): p. 746-8.
- Feldmann, H. and T.W. Geisbert, Ebola haemorrhagic fever. *Lancet*, 2011. 377(9768): p. 849-862.
- CDC. Ebola outbreak in West Africa 2014. 2014; Available from: <http://www.cdc.gov/vhf/Ebola/outbreaks/2014-west-africa/index.html>.
- WHO. Statement on the 1st meeting of the IHR Emergency Committee on the 2014 Ebola outbreak in West Africa. 2014; Available from: <http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/>.
- Chevalier, M.S., et al., Ebola Virus Disease Cluster in the United States - Dallas County, Texas, 2014. *Mmwr-Morbidity and Mortality Weekly Report*, 2014. 63(46): p. 1087-1088.
- Kalra, S., et al., The emergence of ebola as a global health security threat: from ‚lessons learned‘ to coordinated multilateral containment efforts. *Journal of global infectious diseases*, 2014. 6(4): p. 164-77.
- Weingartl, H.M., et al., Transmission of Ebola virus from pigs to non-human primates. *Scientific Reports*, 2012. 2.
- Georges, A.J., et al., Ebola hemorrhagic fever outbreaks in Gabon, 1994-1997: Epidemiologic and health control issues. *Journal of Infectious Diseases*, 1999. 179: p. S65-S75.
- Paessler, S. and D.H. Walker, Pathogenesis of the Viral Hemorrhagic Fevers. *Annual Review of Pathology: Mechanisms of Disease*, Vol 8, 2013. 8: p. 411-440.
- Mahanty, S. and M. Bray, Pathogenesis of filoviral haemorrhagic fevers. *Lancet Infectious Diseases*, 2004. 4(8): p. 487-498.
- Nishiura, H. and G. Chowell, Early transmission dynamics of Ebola virus disease (EVD), West Africa, March to August 2014. *Eurosurveillance*, 2014. 19(36): p. 5-10.
- Mari Saez, A., et al., Investigating the zoonotic origin of the West African Ebola epidemic. *EMBO molecular medicine*, 2015. 7(1): p. 17-23.
- Groseth, A., H. Feldmann, and J.E. Strong, The ecology of Ebola virus. *Trends in Microbiology*, 2007. 15(9): p. 408-416.
- Malloy, C.D. and J.S. Marr, Evolution of the Control of Communicable Diseases Manual: 1917 to 2000. *Journal of public health management and practice : JPHMP*, 2001. 7(5): p. 97-104.
- Koroma, V., Ebola's lost ward (vol 513, pg 474, 2014). *Nature*, 2014. 516(7531): p. 298-298.
- Leroy, E.M., et al., Early immune responses accompanying human asymptomatic Ebola infections. *Clinical and Experimental Immunology*, 2001. 124(3): p. 453-460.
- Baize, S., et al., Inflammatory responses in Ebola virus-infected patients. *Clinical and Experimental Immunology*, 2002. 128(1): p. 163-168.
- Leirs, H., et al., Search for the Ebola virus reservoir in Kikwit, Democratic Republic of the Congo: Reflections on a vertebrate collection. *Journal of Infectious Diseases*, 1999. 179: p. S155-S163.
- Morvan, J.M., et al., Identification of Ebola virus sequences present as RNA or DNA in organs of terrestrial small mammals of the Central African Republic. *Microbes and Infection*, 1999. 1(14): p. 1193-1201.
- Leroy, E.M., et al., Fruit bats as reservoirs of Ebola virus. *Nature*, 2005. 438(7068): p. 575-576.
- Pourrut, X., et al., Spatial and temporal patterns of Zaire ebolavirus antibody prevalence in the possible reservoir bat species. *Journal of Infectious Diseases*, 2007. 196: p. S176-S183.
- Negredo, A., et al., Discovery of an Ebolavirus-Like Filovirus in Europe. *Plos Pathogens*, 2011. 7(10).
- Wittmann, T.J., et al., Isolates of Zaire ebolavirus from wild apes reveal genetic lineage and recombinants. *Proceedings of the National*

- Academy of Sciences of the United States of America, 2007. 104(43): p. 17123-17127.
29. Bermejo, M., et al., Ebola outbreak killed 5000 gorillas. *Science*, 2006. 314(5805): p. 1564-1564.
 30. Leroy, E.M., et al., Multiple Ebola virus transmission events and rapid decline of central African wildlife. *Science*, 2004. 303(5656): p. 387-390.
 31. Ansari, A.A., Clinical features and pathobiology of Ebolavirus infection. *Journal of Autoimmunity*, 2014. 55: p. 1-9.
 32. Fauci, A.S., Ebola - Underscoring the Global Disparities in Health Care Resources. *New England Journal of Medicine*, 2014. 371(12): p. 1084-1086.
 33. Rasmussen, A.L., et al., Host genetic diversity enables Ebola hemorrhagic fever pathogenesis and resistance. *Science*, 2014. 346(6212): p. 987-991.
 34. Bausch, D.G., et al., Assessment of the risk of Ebola virus transmission from bodily fluids and fomites. *Journal of Infectious Diseases*, 2007. 196: p. S142-S147.
 35. Peters, C.J. and J.W. LeDuc, An introduction to Ebola: The virus and the disease. *Journal of Infectious Diseases*, 1999. 179: p. IX-XVI.
 36. Towner, J.S., et al., Rapid diagnosis of Ebola hemorrhagic fever by reverse transcription-PCR in an outbreak setting and assessment of patient viral load as a predictor of outcome. *Journal of Virology*, 2004. 78(8): p. 4330-4341.
 37. Miranda, M.E.G. and N.L.J. Miranda, Reston ebolavirus in Humans and Animals in the Philippines: A Review. *Journal of Infectious Diseases*, 2011. 204: p. S757-S760.
 38. Qiu, X., et al., mAbs and Ad-Vectored IFN-alpha Therapy Rescue Ebola-Infected Nonhuman Primates When Administered After the Detection of Viremia and Symptoms. *Science Translational Medicine*, 2013. 5(207).
 39. Carrion, R., Jr., et al., A small nonhuman primate model for filovirus-induced disease. *Virology*, 2011. 420(2): p. 117-124.
 40. Funk, D.J. and A. Kumar, Ebola virus disease: an update for anesthesiologists and intensivists. *Canadian Journal of Anesthesia-Journal Canadien D Anesthesie*, 2015. 62(1): p. 80-91.
 41. Hofmann-Winkler, H., F. Kaup, and S. Poehlmann, Host Cell Factors in Filovirus Entry: Novel Players, New Insights. *Viruses-Basel*, 2012. 4(12): p. 3336-3362.
 42. Alimonti, J., et al., Evaluation of transmission risks associated with in vivo replication of several high containment pathogens in a biosafety level 4 laboratory. *Scientific Reports*, 2014. 4.
 43. Jahrling, P.B., et al., PRELIMINARY-REPORT - ISOLATION OF EBOLA VIRUS FROM MONKEYS IMPORTED TO USA. *Lancet*, 1990. 335(8688): p. 502-505.
 44. Geisbert, T.W., et al., Pathogenesis of Ebola hemorrhagic fever in cynomolgus macaques - Evidence that dendritic cells are early and sustained targets of infection. *American Journal of Pathology*, 2003. 163(6): p. 2347-2370.



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