Research Highlight

Ebola Virus Disease: General Characteristics, Thoughts, and Perspectives

CHENG Ying, LI Yu, and YU Hong Jie#

In December 2013, a new round of Ebola virus disease (EVD) first occurred in a remote countryside of Guinea and then spread in Guinea, Liberia, Sierra Leone, and Nigeria of West Africa. EVD, caused by Ebolavirus and previously known as Ebola hemorrhagic fever, is an acute infectious disease with fatality rates up to 90%. As of August 22, 2014, the number of suspected and confirmed cases was 2615, causing 1427 deaths[1]. On August 8, 2014, World Health Organization announced the current outbreak in West Africa as an international public health emergency. The global epidemic tendency remains ambiguous to date. In recent years, China closely collaborates with West Africa in labor, business, overseas education, and also sends aid medical team there. Thus, the risk of importing the disease cannot be ignored. We conduct this literature review of epidemiology, pathogen, prophylaxis, and treatment to provide evidence for controlling the risk and carrying out effective interventions.

General Characteristics

Genome As a pathogen of category A, Ebolavirus has powerful pathogenicity and potentiality of biological terrorism. Live particles of this virus should be operated in BSL-4 laboratory. Ebolavirus was first recognized in 1976 to be a non-segmented, enveloped negative-stranded RNA virus of the family Filoviridae. Its uniform diameter is 80 nm, but it can greatly vary in length, up to 14,000 nm. The Ebolavirus genome is 19 kb long, with seven open reading frames encoding structural proteins in the order 3′ leader-NP-VP35-VP40-GP-VP30-VP24-L-5′ trailer, for nucleoprotein, virion protein (VP) 35, VP40, glycoprotein, VP30, VP24, and RNA-dependent RNA polymerase (L). A soluble glycoprotein, the primary product of the GP gene, is secreted in large quantities from infected cells. This glycoprotein is believed to be a determinant of host-cell damages. The genus Ebolavirus can be classified into five species, namely, Sudan ebolavirus (EBOV), Zaire ebolavirus (EBOV), Taï Forest ebolavirus (TAFV), Bundibugyo ebolavirus (BDBV), and Reston ebolavirus (RESTV). Since 1976, Ebolavirus has slightly evolved every year, and undergone several mutations in the past 40 years. Phylogenetic analysis of the full-length genome sequences established a separate clade for the new Guinean EBOV strain, which is considered as the causative agent for the current outbreak in West Africa and its homology with other known EBOV strains is 97%[2]. This finding suggests that the EBOV strain from Guinea shares a recent ancestor with the strains from the Democratic Republic of Congo and Gabon but has not been introduced from the latter countries into Guinea.

Epidemiology EVD remains a plague in Africa, with an increase in the number of outbreaks and cases since 2000. As a classic zoonosis, Ebolavirus is believed to persist in a reservoir species in endemic areas. Apes, man, and perhaps other mammalian species are regarded as end hosts of Ebolavirus[3]. Bats are currently thought as potential reservoir species. After direct contact with virus in dead or infected wildlife and the subsequent person-to-person transmission, Ebolavirus enters the body through mucosal surfaces or skin abrasions. EVD symptoms usually appear after an 8-to-10-day incubation period. Patients initially show nonspecific flu-like symptoms, such as fever, chills, malaise, muscle pain, and headache. A macropapular rash associated with varying severity of erythema often appears around day 5 and serves as a characteristic feature. Extensive viral replication causes systemic, vascular, and neurologic manifestations, and necrosis occurs in the liver, spleen, kidneys, and gonads. In fatal cases, death occurs usually between 6 and 16 days after infection, and multiple organ failure and severe syndrome might resemble the fatal septic shock.

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Division of Infectious Disease, Key Laboratory of Surveillance and Early-warning on Infectious Disease, Chinese Center for Disease Control and Prevention, Beijing 102206, China

Pathogenic Mechanism The target host cells of Ebola virus are hepatocytes, endothelial cells, macrophages, dendritic cells, etc. Infected monocytes and macrophages release proinflammatory cytokines and chemokines, including tumor necrosis factor, interleukin-1β, and reactive oxygen and nitrogen species. These mediators attract neutrophils, which might release further mediators for vasodilation and increased vascular permeability. The inhibitory effect on innate immune function may be presented by the resistance of interferon, which interrupts the critical interferon response pathways by the virus itself. The VP24 of Ebola virus might interrupt the nuclear accumulation of the protein signal transducer and activator-1, which blocks type-I interferon signaling and confers insensitivity to antiviral response. Ebola VP35 blocks the activity of interferon regulatory factor 3, thereby decreasing interferon responses. VP35 counteracts the activity of the double-stranded RNA-dependent protein kinase. Meanwhile, dendritic cells (DCs) are a critical link between innate and adaptive immune responses to many pathogens[4]. After infection, human DCs fail to secrete the normal profile of proinflammatory cytokines and costimulatory molecules to become mature. Thus, they fail to upregulate major histocompatibility complex molecules and thus fail to stimulate T cells. Conversely, lymphocytes undergo massive apoptosis in infected humans and nonhuman primates to cause compromised adaptive immunity. Although lymphocytes are not targets of the virus, substantial numbers of these cells undergo apoptosis by the TRAIL and Fas-FasL pathways, and the numbers of CD4+ and CD8+ T cells are substantially reduced before death. The release of inflammatory mediators increases vascular permeability[5], and the viral envelope glycoprotein GP acts as a major determinant of vascular cell injury. Thus, fatal Ebolavirus infection is characterized by broad immunosuppression because of an aberrant nonspecific and deleterious innate immune response and little or no stimulation of an antigen-specific adaptive response. Therefore, immunity pathology plays an overwhelming role in the fatal infection process of the virus.

Treatment and Prevention Licensed antiviral drugs and vaccines for Ebolavirus remain unavailable to date. The drugs under development or phase I clinical trials include the anti-influenza drug T705, the optimized 'cocktail' therapy ZMapp, RNA-polymerase inhibitors, small interfering RNA nanoparticles, and recombinant modulators. T705 is an adenosine analog that may prevent virus replication. The efficacy of ZMapp should be withheld for only two cases[6]. RNA-polymerase inhibitors and small interfering RNA nanoparticles inhibit protein production. The protective effect of immunoglobulins remains uncertain. A recent report has indicated that transferring the neutralizing human monoclonal antibody KZ52 cannot control infection in a macaque model[7]. The usefulness of an Ebolavirus vaccine was disputed because of the disease's rarity, little interest by the industry, and the potential cost. Vaccines under development include post-exposure and pre-exposure vaccination. The balance between efficacy and safety is also a great concern.

Thoughts and Perspectives

Several acute and dangerous agents have even been reminded because of the high lethality of this pathogen. Similar to the 1918 influenza, the host immune response to Ebolavirus is characterized by an aberrant interferon response and abnormally high levels of cytokines and chemokines[8]. In addition, the same overwhelming viremia, i.e., lack of control by the innate immune response and failure to develop adaptive immunity, has been observed with the severe acute respiratory syndrome coronavirus, Marburg virus, Lassa fever virus, etc. However, lethal, acute pathogens tend to kill rapidly before the adaptive immune response. Moreover, Ebolavirus shares some similar pathogenic mechanism, i.e., lymphocyte apoptosis, as human immunodeficiency virus. All the profiles mentioned above classify Ebolavirus as a 'natural perfect killer,' which hinders the clinical prevention and control of EVD.

Present knowledge is principally based on infections with Zaire Ebolavirus, the most pathogenic species, and on studies involving nonhuman primates. The species involved should be clearly understood before applying postexposure vaccination based on vesicular stomatitis virus because little cross-protection exists between the various Ebolavirus species; otherwise, such vaccination cannot confer efficient protection. Therefore, future efforts should focus on the knowledge gaps about other species of Ebolavirus. The ecology of reservoir species and their infection status and shedding mechanisms should also be elucidated through field studies to prevent primary transmission from reservoir species to man. Detailed investigations should also be conducted to determine how the ecological cycle of Ebolavirus can be disrupted and how the virus is transferred to

humans. The mechanism underlying lymphocyte apoptosis is also unknown. Ebola virus does not target lymphocytes, but their numbers are rapidly exhausted once viral titers are measurable in the host. The role of cytokine storm versus direct viral cytotoxicity to endothelial cells remains the subject of further speculation. These topics should be given attention to open new targets for intervention strategies.

EVD's epidemic also indicates that traditional customs contribute to the spread of infectious diseases[9]. A close linkage also exists between anthropology and public health. In this epidemic status, clinic staff are at high risk for EVD, thus reflecting the importance of infrastructure construction and the standard operation protocol in healthcare-associated infections[10]. Therefore, strengthening the support and surveillance in areas and populations with scarce resources will benefit the global public health.

#Correspondence should be addressed to YU Hong Jie, Tel: 86-10-58900548, Fax: 86-10-58900576, E-mail: yuhj@chinacdc.cn

Biographical note of the first author: CHENG Ying female, born in 1975, MD&PhD, associate professor, majoring in healthcare-associated infectons.

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