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Review Article

Ebola Hemorrhagic Fever

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Abstract

Ebola virus disease (EVD) also known as Ebola haemorrhagic fever is a severe contagious disease affecting humans and non-human primates. It is usually transmitted to humans through direct contact with blood, tissue, body fluids and secretions from an infected animal or human. The causative agent is classified in the genus Ebolavirus of the Filoviridae family. Filoviruses are filamentous enveloped viruses containing a non-segmented, negative-strand genomic RNA of approximately 19 kilobases. Patients are diagnosed by testing of body fluids and serum with an ELISA test / PCR; however the results are not always accurate. There is currently no treatment for Ebola hemorrhagic fever. Vaccines are in clinical trials and hold the future in preventing this disease. Ebola is on the United States' list of possible bioterrorism agents because no humans have been found to have immunity to it.

Background

Ebola is a member of the Filoviridae viral family, characterized by the long, thin filaments it is a RNA virus (19-kb negative-sense) which codes for seven proteins. The seven filoviral proteins are the glycoprotein (GP), the polymerase (L), the nucleoprotein (NP), a secondary matrix protein (VP24), the transcriptional activator (VP30), the polymerase cofactor (VP35), and the matrix protein (VP40). It was first discovered near the Ebola River and was named accordingly. Filoviruses are infrequently encountered, and their natural history is only now being understood. Because of the lack of predictive information about them, and serious human disease they cause, they require our attention. Filoviruses cause a severe, unrelenting viral hemorrhagic fever with high mortality [1, 2, 3]. Discovered in late 1970s, the international community was startled as it caused major outbreaks of hemorrhagic fever in the Democratic Republic of the Congo (DRC) [4] and Sudan [5].

Outbreaks chronology

Ebola virus was first discovered in 1976 when an outbreak of Ebola hemorrhagic fever occurred in Zaire in Democratic Republic of the Congo (DRC) [6]. Since then five different strains of Ebolavirus have been discovered, namely Zaire ebolavirus (EBOV), Sudan ebolavirus (SUDV), Tai Forest ebolavirus (TAFV), Bundibugyo ebolavirus (BDBV) and Reston ebolavirus (RESTV),with fruit bats considered as the most likely reservoir host [7].

The Zaire Ebola virus has one of the highest fatality rates of any pathogenic virus affecting

humans. In the 1976 outbreak, it killed 88 percent of patients, 81 percent in 1995, 73 percent in 1996, 80 percent in 2001-2002, and 90 percent in 2003, although none of these outbreaks were as large as the original [6]. However March 2014-Present outbreak involving multiple countries in Africa has reported a total of 21206 cases and 8386 deaths [8].

Sudan Ebola virus had a fatality rate of 53 percent in 1976, 65 percent in 1979, 53 percent in the over 400 patients infected in 2000, 41 percent in 2004, 36.4% in June-October 2012 and 50% in November 2012-January 2013 which occurred in Uganda [6, 9].

Ivory Coast Ebola (TAFV) virus was first discovered in 1994 when a scientist conducting autopsies on chimpanzees contracted Ebola hemorrhagic fever. This has been the only case of Ivory Coast Ebola known to have occurred in humans [6].

In 1989 Crab-eating macaques that were imported from the Philippines to Reston, Virginia were found to have a virus similar to Ebola. Around 6 out of 150 animal handlers developed antibodies to this virus, however none of which actually developed Ebola hemorrhagic fever. It was later classified as Reston Ebola virus and CDC concluded that this strain had a low infection rate for humans [6]. Other episodes occurred in Italy in 1992 and in the United States in 1996. All these events were traced to the facility of a single exporter, but the ultimate source of the virus has never been ascertained, although Mindanao was the origin of the monkeys taken for conditioning and resale. In 2009, an outbreak of Reston Ebola virus was discovered in pigs in the Philippines, and antibody evidence of human infection was also found however the source has not been found [10].

In November 2007, CDC confirmed EHF in diagnostic samples associated with an outbreak of illnesses with unknown etiology in Bundibugyo District, Uganda. Genetic sequencing demonstrated that infections were caused by a novel fifth Ebolavirus species, BEBOV [11], marking the first time a new filovirus species had been identified since 1994 [12] mortality rate being 25%. Then in June-November 2012 another outbreak occurred in Democratic Republic of Congo having a mortality of around 36% [9].

Epidemiology and Transmission

EVD occurred mainly in the rainforest areas of Central Africa (DRC, Sudan, Gabon, and Uganda) up to 2013. *Taï Forest ebolavirus* (TEBOV) affected only West Africa in 1994. The severe epidemics, starting in 2013-14, affected a large West African region (Guinea, Sierra Leone, and Liberia) with imported cases in Nigeria and Senegal. Another alarming event is that the epidemics penetrate densely populated areas including capital cities.

Ebola is transmitted through body fluids and / or direct contact with infected individuals. It is believed to spread to human populations through contact with infected primates, as opposed to directly from natural reservoirs. Fruit bats are the suspected natural sources of the virus. They themselves are asymptomatic but have been found to carry the virus, making them good candidates for natural reservoirs.

Transmission of Ebola virus among non-human animals is a little different. It is proposed that after partially eating the fruits, fruit bats drop these fruits that carry viruses in the bat saliva. Gorillas or other monkeys then eat the fruit, and therefore the virus as well. Decomposing bodies only remain infectious for three to four days after death, and gorillas do not typically interact among different groups, which mean the victims were probably infected by several animal host reservoirs [7]. In addition to high titres of virus in blood, the skin of patients, including fibroblasts and other dermal structures, is extensively infected [13]; this probably accounts for the additional risk to those participating in traditional burial preparation of the cadaver [4] and mourners touching the cadaver [14]. Nevertheless, Ebola has been shown to spread through the air under carefully controlled laboratory conditions [15].

Pathogenesis

Ebola virus disease has findings that are similar in human patients and nonhuman primate models. Viremia occurs in the acute period, and its disappearance is marked by clinical improvement and usually the appearance of antibodies in blood [16]. Humoral immune response is probably not effective because passive convalescent antibody transfer does not protect against experimental inoculation [17, 18]. Possible explanations for the failure to mount an effective immune response in fatal cases include the presence of a putatively immunosuppressive amino acid sequence in the filovirus glycoprotein [19], the secretion of a soluble glycoprotein by Ebola virus–infected cells [20], and the extensive lymphoid damage evident in postmortem examination [21]. In addition, Ebola-infected cells have a deficient response to added

interferon [22, 23], induction of the antiviral state, and induction of interferon or activation of downstream pathways. One major filovirus protein, VP35, is known to be responsible for the latter [24].

Clinical features

The incubation period of EVD in humans is usually 2-21 days [25]. Ebola virus begins to effect infected individuals with flu-like symptoms like fever, myopathy, and headache, followed by hemetemesis and diarrhoea, nausea and vomiting, anorexia, body weakness, abdominal pain, arthralgia, back pain, mucosal redness of the oral cavity, dysphagia, conjunctivitis, rashes on the body [26].

As the disease progresses, wasting becomes evident, and bleeding manifestations such as petechiae, hemorrhages, ecchymoses around needle puncture sites, and mucous membrane hemorrhages occur in half or more of the patients. Around day 5, most patients develop a maculopapular rash, prominent on the trunk. In the second week, the patient defervesces and improves markedly or dies in shock with multiorgan dysfunction, often accompanied by disseminated intravascular coagulation, anuria, and liver failure. Convalescence may be protracted and accompanied by arthralgia, orchitis, recurrent hepatitis, transverse myelitis, or uveitis [17].

Diagnosis

General approach

The approach to evaluating patients with possible Ebola virus disease depends upon whether or not the individual displays appropriate signs and symptoms, how likely it is that the exposure will result in disease (ie, the level of risk), and when the exposure occurred.

1. Patients who present with signs and symptoms consistent with Ebola virus disease should be immediately assessed to determine their risk of exposure to Ebola virus [27].

- For all symptomatic patients who may have been exposed to Ebola virus, infection control precautions should be used and also for patients in whom risk of exposure is unclear at the time of their initial presentation, until a medical evaluation can be performed.
- Testing for Ebola virus should generally be performed for patients who have symptoms consistent with Ebola virus disease and have had an exposure that puts them at risk.

2. Asymptomatic individuals with a possible exposure to Ebola should be monitored so that they can be isolated if signs or symptoms occur.

Indications for initial testing for Ebola virus infection

All patients with suspected Ebola virus disease should be evaluated in conjunction with local and state health departments [28-30].

- Testing for Ebola virus infection is performed in symptomatic patients with any possible risk of exposure to Ebola virus (high, some, or low risk).[27]
- In patients who have an identifiable risk but no signs or symptoms of Ebola virus disease testing is not warranted. These patients should be monitored and tested if they become ill.
- Testing is not warranted for patients without any identifiable risk of exposure to Ebola virus.

Laboratory diagnosis

The laboratory diagnosis of Ebola virus infection is made by the detection of viral antigens or RNA in blood or other body fluids and by viral isolation.

Diagnostic tests

For Ebola virus infection rapid diagnostic tests are the most commonly used tests for diagnosis.

- Most acute infections are diagnosed through the use of RT-PCR which generally detects viral RNA within three days after the onset of symptoms [31, 32].
- For patients with symptoms for fewer than three days duration repeat testing may be needed [32].
- A negative RT-PCR test that is collected e”72 hours after the onset of symptoms rules out Ebola virus disease [31, 33].
- The demonstration of genetic diversity and rapid accumulation of sequence changes of Ebola virus in the West African epidemic indicates that careful monitoring will be needed to ensure the continued sensitivity of RT-PCR diagnostics [34].

- In past outbreaks, testing for viral antigens by enzyme-linked immunosorbent assay (ELISA) was also frequently performed [20, 35-40].
- IgM antibodies detection by capture ELISA is useful in early convalescence [16]. IgG serologic testing has not been reliable. When an indirect fluorescent antibody test is applied, false-positive and irreproducible results are common. For this reason, confirmation, even of apparent seroconversions, is desirable. The IgG ELISA appears to have decreased this problem but still requires further verification [17, 41].

Timeline of Infection	Diagnostic tests available
Within a few days after symptoms begin	Antigen-capture enzyme-linked immunosorbent assay (ELISA) testingIgM ELISAPolymerase chain reaction (PCR)Virus isolation
Later in disease course or after recovery	IgM and IgG antibodies
Retrospectively in deceased patients	Immunohistochemistry testing PCR Virus isolation

Other laboratory findings

Patients with Ebola virus disease typically develop leukopenia, thrombocytopenia, and serum transaminase elevations, as well as renal and coagulation abnormalities. Other findings include a marked decrease in total plasma protein (reflective of a capillary leak syndrome) and elevated amylase levels [42].

Current Treatments

1. Supportive Care

Since there are currently no FDA-approved treatment strategies the current clinical standard for filoviral infection is supportive care. It consists of oral fluid rehydration, oral medication, nutritional supplementation, and psychosocial support [43]. Nasogastric feeding tubes and i.v. administration of both fluids and medication are increasingly considered supportive care where possible during outbreak scenarios to prevent dehydration and facilitate support of blood pressure [43, 44]. Platelet transfusion and replacement of coagulation factors is indicated. Heparin or other treatment should be used for treatment of DIC. In the severe Zaire Ebola virus monkey model, activated protein C improves survival, and this licensed drug should be considered for human therapy [45]. In addition, a recombinant inhibitor of the tissue factor–activated factor VII complex {recombinant nematode anticoagulant protein c2 (rNAPc2)} improves survival and should also be considered [46].

2. Immunotherapy

Transfer of immune serum for the treatment of filovirus infection in humans has previously been attempted. However, interpretation of these results has been cautious due to the study conditions as well as the uncertainty of the disease stage at which the individuals were treated [47]. As a result, much attention has focused on animal studies evaluating candidate products. Both polyclonal and monoclonal passive therapies have been shown to be efficacious in rodents for filovirus infection [27, 48, 49]. These sources of monoclonal antibodies have ranged from murine monoclonal antibodies to recombinant-derived cloned human monoclonal antibodies from survivors of filovirus infection [27, 50].

Vaccines

A DNA vaccine prepared against glycoprotein (GP) induces protective cellular immunity against Zaire strain challenge in guinea pigs but not in monkeys [18]. A vesicular stomatitis virus–based construct using Ebola Zaire GP successfully protected mice and monkeys, including postexposure treatment in some settings [51]. While this type of construct has never been used in humans, no ill effects were seen. A prototype adenovirus vaccine expressing this antigen has successfully protected monkeys and demonstrated a good safety profile in phase I studies in humans [52, 53]

Prevention

If you travel to or are in an area affected by an Ebola outbreak, make sure to do the following:

- Practice careful hygiene. For example, wash your hands with soap and water or an alcohol-based hand sanitizer and avoid contact with blood and body fluids.
- Avoid funeral or burial rituals that require handling the body of someone who has died from Ebola.

- Avoid contact with bats and nonhuman primates.
- Avoid facilities in West Africa where Ebola patients are being treated.
- After you return, monitor your health for 21 days and seek medical care immediately if you develop symptoms of Ebola.
- Healthcare workers who may be exposed to people with Ebola should follow these steps:
- Wear appropriate personal protective equipment (PPE).
- Practice proper infection control and sterilization measures.
- Isolate patients with Ebola from other patients.
- Avoid unprotected contact with the bodies of people who have died from Ebola.
- Notify health officials if you have had direct contact with the blood or body fluids, of a person who is sick with Ebola.

Conclusion

The main goals currently being addressed with Ebola virus are finding ways of treatment for Ebola hemorrhagic fever and finding safe and effective vaccines for the virus that can be applied to humans. If an approved vaccine could be developed for Ebola virus, it would save many people from the painful effects of Ebola hemorrhagic fever. Although it is not a problem right now for most populations outside of Africa, Ebola virus has the potential to be dangerous from the point of view of global health in the future. With more research and a greater understanding of the virus, Ebola will hopefully become a less pressing matter in global health.

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