A review on Ebola virus disease

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Abstract- **Ebola virus is transmitted to people as a result of direct contact with body fluids containing virus of an infected patient. The incubation period usually lasts 5 to 7 d and approximately 95% of the patients appear signs within 21 d after exposure. Typical features include fever, profound weakness, diarrhoea, abdominal pain, cramping, nausea and vomiting for 3-5 days and maybe persisting for up to a week. Laboratory complications including elevated aminotransferase levels, marked lymphocytopenia, and thrombocytopenia may have occurred. Hemorrhagic fever occurs in less than half of patients and it takes place most commonly in the gastrointestinal tract. The symptoms progress over the time and patients suffer from dehydration, stupor, confusion, hypotension, multi-organ failure, leading to fulminant shock and eventually death. The most general assays used for antibody detection are direct IgG and IgM ELISAs and IgM capture ELISA. An IgM or rising IgG titter (four-fold) contributes to strong presumptive diagnosis. Currently neither a licensed vaccine nor an approved treatment is available for human use. Passive transfer of serum collected from survivors of Junín virus or Lassa virus, equine IgG product from horses hyper vaccinated with Ebola virus, a "cocktail" of humanized-mouse antibodies (ZMapp), recombinant inhibitor of factor VII a/tissue factor, activated protein C, RNA-polymerase inhibitors and small interfering RNA nano particles are among the therapies in development.**

Index terms- **Ebolavirus, Epidemiology, Pathophysiology, Treatment**

INTRODUCTION

Ebola virus disease (EVD), or simply Ebola, is a viral haemorrhagic fever of humans and other primates caused by ebolaviruses. Signs and symptoms typically start between two days and three weeks after contracting the virus with a fever, sore throat, muscular pain, and headaches. Vomiting, diarrhoea and rash usually follow, along with decreased function of the liver and kidneys. At this time, some people begin to bleed both internally and externally. The disease has a high risk of death, killing 25% to 90% of those infected, with an average of about 50%. This is often due to low blood pressure from fluid loss, and typically follows six to 16 days after symptoms appear.

The virus spreads through direct contact with body fluids, such as blood from infected humans or other animals. Spread may also occur from contact with items recently contaminated with bodily fluids. Spread of the disease through the air between primates, including humans, has not been documented in either laboratory or natural conditions. Semen or breast milk of a person after recovery from EVD may carry the virus for several weeks to months. Fruit bats are believed to be the normal carrier in nature, able to spread the virus without being affected by it. Other diseases such as malaria, cholera, typhoid fever, meningitis and other viral haemorrhagic fevers may resemble EVD. Blood samples are tested for viral RNA, viral antibodies or for the virus itself to confirm the diagnosis.

ETIOLOGY

Viral hemorrhagic diseases, caused by members of the Flaviviridae, Bunyaviridae, and Arenaviridae viral families, are characterized by fever and bleeding diathesis, followed by circulatory collapse and death. Flaviviridae family viruses are responsible for yellow fever and dengue fever. A Bunyaviridae family virus is responsible for Crimean-Congo hemorrhagic fever. An Arenaviridae family virus is responsible for Lassa fever. These diseases have resulted in considerable morbidity and mortality for hundreds of years if not millennia. Beginning approximately 50 years ago, viral hemorrhagic disease caused by previously unrecognized viruses, Marburg virus and Ebola virus, began to appear.

Marburg virus is comprised of 1 species within the genus Marburgvirus. Ebola virus consists of 5 viral species within the genus Ebolavirus. Ebolavirus and Marburgvirus comprise 2 of the 3 genera in the

family Filoviridae. The third genus in the Filoviridae family is Cueva virus, which does not appear to cause human disease. Filoviridae are in the order Mononegaviruses (Table 1).6 Viruses within the order Mononegaviruses are encapsulated single-stranded, negative-sense (-polarity) RNA viruses. The negative-sense RNA must first be converted to a positive-sense RNA within a cell before the gene frames encoded in the RNA can be read, producing messenger RNA, responsible for the production of viral proteins on ribosomes.

Taxonomy of Ebolavirus & Marburgvirus	
Order: Mononegaviral	
Family: Filoviridae	
Genus: - Ebolavirus Species: - - Bundibugyo ebolavirus - Reston ebolavirus - Sudan ebolavirus - Tai Forest ebolavirus - Zaire ebolavirus	Genus: - Marburgvirus Species: - Marburgvirus marburgvirus[b]

EPIDEMIOLOGY

Filoviruses have been in existence for >10 million years.7 Marburg and Ebola viruses diverged a common ancestor >10,000 years ago.8 The first documented illness caused by 1 of the 2 hemorrhagic fevers was in August 1967.9 Laboratory workers in a commercial facility in Marburg, Germany, a town just north of Frankfurt, Germany, became ill after working with African green monkeys (Cercopithecus aethiops) imported from Uganda. Other laboratories that had received shipments of the monkeys, which were to be used in polio vaccine production, were contacted. In 2 of the laboratories, 1 in Frankfurt and 1 in Belgrade, laboratory personnel also had become infected from the monkeys. Thirty-seven people ultimately contracted the illness, 9 of whom died. Their illness was manifested by fever, vomiting, diarrhoea, bleeding, and circulatory shock. Virologists in Germany identified a virus that was a member of the family Filoviridae that had a unique structure. Some of the virions were long filamentous particles that measured as much as 14 μm in length and were 80 nm wide. Other virions were curved, resembling the number 6, or a hairpin10 (Fig. 1).
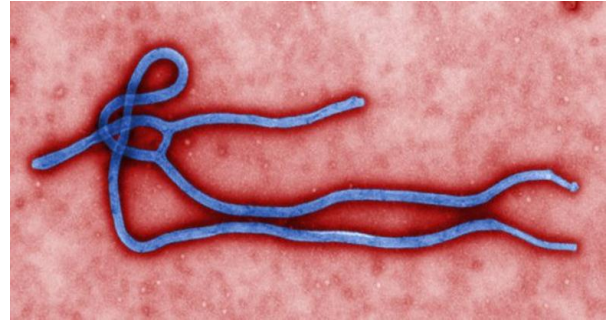

Fig. 1 Ebola virus virion. Created by Centers for Disease Control and Prevention microbiologist Cynthia Goldsmith, this colorized transmission electron micrograph revealed some of the ultrastructural morphology displayed by an Ebola virus virion

On the basis of the available evidence, WHO hypothesized that someone from southwest Sudan who was either acutely ill with the disease, or convalescing from it, and who travelled to northeast Zaire to seek medical care was the index case. On the basis of the symptoms, the index patient might have received a parenteral injection of chloroquine. If so, the injection would have contaminated the needle, which might have been used on several more patients, thus spreading the disease. However, this theory was dispelled by the discovery that the epidemic that appeared in southwest Sudan was caused by a virus from a different species than the one that caused disease in that appeared in Zaire.

PATHOPHYSIOLOGY

Ebola virus is most commonly transmitted when secretions from an infected patient come in contact with mucosa or conjunctiva or via percutaneous injury (e.g., a laceration or abrasion). There are no human data, but data from cynomolgus monkeys show that an IM injection of as few as 10 plaque forming units (each plaque-forming unit is assumed to represent 1 virion) results in lethal Ebola virus disease within 8 to 12 days of receiving the injection. Increasing the IM dose to 1000 plaque-forming units resulted in death within 5 to 8 days. Ebola virus replication requires attachment to a cell's membrane, binding to specific cell receptors, and fusion with the cell's membrane. The virion's glycoprotein outer capsule is responsible for the attachment of the virus to the cell (Fig. 2)
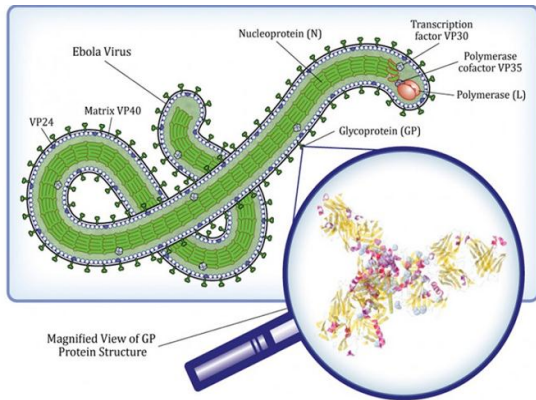
Fig. 2 Ebola virus and proteins on its surface that may provide targets for new drugs that could help treat or prevent Ebola infections

Several molecules have been proposed that function either as a receptor on a cell's surface or as a mediator to facilitate viral entry into a cell, including C-type lectins, tyrosine kinase receptors, β1 integrin receptors, and Niemann Pick C1 proteins.Takada et al have argued that, based on Ebola virus's pantropism, the virus likely uses several different C-type lectins to gain entry into a variety of cells. Because of the virus's marked selectivity for specific cells, some of the proposed receptors are unique to those cells (e.g., dendritic cell−specific intercellular adhesion molecule3-grabbing nonintegrin) or human macrophage galactose- and N-acetyl galactosamine-specific C-type lectin).There also has been speculation that Ebola virus does not fuse to a cell's membrane but rather activates the cell's endocytic mechanisms, acting as a "Trojan horse" to gain entry into the cell's cytoplasm. However, the most recent evidence suggests that the virus fuses to the cell membrane through glycoprotein 2, which can undergo conformational changes between an alpha helix and a beta layer to insert itself into the lipid bilayer that comprises the cell membrane. Once Ebola virus gains access to the interior of the cell, viral RNA and 7 proteins including MP, VP35, VP30, glycoprotein, and L are released into the cell's cytoplasm.10 Glycoprotein makes up the virus's outer coat and is involved in the binding of virus to cell surface receptors. The L protein is an RNA polymerase that translates Ebola virus's negative-sense RNA into positive-sense messenger RNA from which Ebola virus's structural proteins are generated. In addition, because the RNA is a copy of the negative-sense Ebola virus RNA, it serves as a template for replication of Ebola virus's RNA. The structural proteins and genomes congregate in the cytoplasm near the cell membrane, where they reassemble into new virions, after which they are released by the cell.

SYMPTOMS

Primary signs and symptoms of Ebola often include some or several of the following:
- Fever
- Aches and pains, such as severe headache, muscle and joint pain, and abdominal (stomach) pain
- Weakness and fatigue
- Gastrointestinal symptoms including diarrhea and vomiting
- Abdominal (stomach) pain
- Unexplained hemorrhaging, bleeding or bruising

Other symptoms may include red eyes, skin rash, and hiccups (late stage).

Many common illnesses can have the same symptoms as EVD, including influenza (flu), malaria, or typhoid fever.

TREATMENT

Not only are there no known treatments for Ebola virus disease, but very little is known about the mechanisms by which patients develop shock and DIC. The epidemics that have occurred during the past 4 decades have been in low-income countries with limited health care resources. Most patients do not have simple laboratory tests, such as a complete blood cell count, and more costly tests, such as a coagulation panel or cardiac output measurement, are rare. In addition, tests must be performed in a biosafety level-4 laboratory. What we know has been learned from past epidemics and studies in nonhuman primates. Treatment is supportive. Dehydration is very common, so rehydration should be attempted with an oral balanced electrolyte solution.

If the patient cannot maintain fluid balance because of gastrointestinal illness, IV crystalloid fluids should be administered. Hypoxia is reported to occur with Ebola virus disease, but during the current epidemic, it is not as common as one might expect unless the patient develops multisystem organ dysfunction. There are no predictors of survival. However, as was observed in the nonhuman primate studies, the

greater the viral exposure, the shorter the incubation period, and the greater likelihood of death. Therefore, anyone who develops symptoms within 3 to 5 days of contact with an infected patient will likely have a worse outcome than someone who becomes symptomatic after many days.

Other therapies are being investigated to treat Ebola virus disease, including the inhibition of membrane fusion by the virus (T-20 Enfuvirtide), transcription/replication inhibitors, nucleoside analogs, antisense oligonucleotides, small-interfering RNAs, maturation inhibitors to include furin inhibitors and budding inhibitors, and modulation of the cytokine storm by a variety of cytokine inhibitors.

CONTROL

Missair et al. have presented information on how anaesthesiologists should provide care to patients with Ebola virus disease. The current pandemic will only be brought under control with the use of the same techniques and methods that have worked in past epidemics of Ebola virus disease: early diagnosis (so that patients can be more quickly isolated), contact tracing to identify at-risk individuals and limit their contacts, patient isolation, and strict (and better) infection control procedures.

CONCLUSION

The current Ebola virus disease pandemic has lasted longer, affected more individuals, killed more patients, and created more social havoc than all previous Ebola virus disease epidemics combined. However, to put the current pandemic in context, viral hemorrhagic fevers in to affect >100 million and kill 60,000 annually. Ebola virus disease has caused so much disruption because so little is known about it because of its high mortality and because of its clinical manifestations. However, the current pandemic has not occurred because Ebola virus has mutated but, rather, because a lack of information (avoidance of bats and infected nonhuman primates), inadequate public health practices (protocols for isolation and implementations of quarantines and unsafe burial practices), ease of travel, insufficient infection control and poor health care education. On the basis of past experience, it is likely that 1 year from now nothing will have changed. However, on the basis of what we have learned, we as anaesthesiologists should take the necessary steps now to better prepare and educate ourselves so that we can protect our families from the sequelae of such events and provide effective treatment for those to whom we will provide care during this and subsequent epidemics.

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