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REVIEW ARTICLE - 2

Knowing Ebola: The Beast From The Bats!

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Introduction: : Ebola is one of the most lethal virus that infects primates. Endemic to Africa and to Philippines[1]. This virus was first recognised in 1976, when two unrelated Ebola Haemorrhagic Fever (EHF) outbreaks occurred 800 km apart Northern Zaire (Yambuku) & Southern Sudan (Nzara or Maridi)

It was named as "EBOLA" after the small river near the catholic mission of Yambuku, the epicenter of 1976, EHF outbreak.

Ebola Haemorrhagic Fever (EHF) is an acute viral syndrome that present with fever & an ensuing bleeding diathesis that is marked by high mortality in human & nonhuman primates. The fatality rates are in between 50% to 100%. Due to its lethal nature, this Filovirus is classified as a biological class 4 pathogen (HIV is Biosafety level 2 pathogen)[2].

Etiology : Ebola virus belongs to the family *Filoviridae*, in the order *Mononegaviriales,* which includes *Rhabdoviridae & Paramyxoviridae.*

The virion is pleomorphic, producing 'U' shaped, '6' shaped or circular forms. It consists of a single molecule of linear single stranded, negative sense RNA of 4.2 x 106 Da.

Ebola virus disease (EVD) is caused by four out of five viruses classified in the genus Ebola virus. The four human disease causing viruses are Bundibugyo virus (BDBV), Sudan virus (SUDV), Tai Forest virus (TAFV), & the one called Ebola virus (EBOV), formerly Zaire Ebola virus. The fifth virus Reston virus (RESTV) is thought to be non pathogenic for humans.

These all are closely related to Murburg viruses[3].

Transmission : Ebola virus disease is believed to have been occurred after an Ebola virus was transmitted to an initial human by contact with an infected animals body fluids. Human to human or animal to human contact can be through direct contact with infected blood or bodily fluids (even while embalming infected dead person) [3] or by contact with contaminated medical equipments, like needle, syringes or other instruments. Health care workers (HCW) can get infected if they do not practice universal safety precautions like wearing aprons, gloves, mask, cap, hand washing, eye gears. Air born transmission have not been documented. Bats drop particularly eaten fruits & pulp, then land mammals such as gorilla & duikers feed on these fallen fruits. This chain of events forms a possible direct/indirect way of transmission from natural reservoir / host to the animal population. This virus can remain in decomposing bodies for 3 to 4 days. The potential wide spread of infection is considered very low as infection can only be transmitted by direct contact with infected material or blood or bodily fluids. Semen may be infectious in survivors for upto 50 days. Quick onset of the disease and easier identification can limit the individual from spreading it to the community [4].

Reservoir : Bats are considered the most likely natural reservoir of the EBOV. Plants, arthropods & birds also serve as the reservoir. The first cases of EBOV outbreak were from a cotton factory in 1976 & 1979 and bats were residing in the factory. Bats have also been implicated in Marburg virus infections in 1975 and 1980. Out of 24 plant species and 19 vertebrate species only bats became infected and remained clinically asymptomatic as a characteristic of reservoir species.

Signs and symptoms :

Typically, Ebola virus Infection runs its course within 14-21 days .[5] The average time between contracting the infection and start of signs and symptoms (incubation period) is 8-10 days, but can vary from 2-21 days.

Infection initially present with non specific symptoms such as fever, myalgia, malaise, headache, joint and muscle pain and abdominal pain, vomitting, diarrhea and loss of appetite are common[4]. Skin manifestations may include a maculopapular rash (50% of cases)[4]. Early signs and symptoms may mimic the infectious diseases like influenza, malaria, non typhoidal salmonellosis, fulminanat hepatitis, Sepsis, Dengue fever, various forms of encephalitis, yellow fever, lassa fever, marburg and other haemorrhagic diseases[3].

As the infection become evident and progresses, patient exhibits bleeding and coagulation abnormalities [5]. In 40-50% of cases, bleeding from punctures sites and mucous membrane (e.g. gastrointestinal tract, nose, vagina & lungs) may occur.

Bleeding phase starts 5-7 and days after initial phase of signs and symptoms. Internal bleeding may present by reddening of eyes and blood in vomit. Bleeding into skin by petechiae, purpura, ecchymoses & hematomas (especially around needle injection site) [4]. These abnormalities may lead to hematological irregularities such as lymphopenia and neutropenia. Cytokines are released when reticulo-endothelial cells are encounter with viruses which can contribute to exaggerated inflammatory responses that are not protective. Damage to liver combined with massive viremia leads to disseminated intravascular coagulopathy[5], neuro-psychiatric manifestations, prostration, delirium, confusion, comma, cardiovascular distress and hypovolemic shock leading to death may occur.

Pathophysiology : Endothelial cells, mononuclear phagocytes and hepatocytes are main targets of infection [4]. After infection Ebola virus glycoprotein is synthesized in secreted (sGP) or full length transmembrane (GP) form and each gene product has distinct biochemical and biological properties e.g. GP appears to form a trimeric complex [6] and binds preferentially to endothelial cells lining the interior surface of blood vessels whereas sGP does not [7]. This binding of trimer interferes with the signaling of neutrophils, a type of white blood cells, which allows the virus to evade the immune system by inhibiting early steps of neutrophil activation. These white blood cells carry the virus to places like lymph nodes, liver, lungs and spleen. These white blood cells also serve as carriers to transport viruses throughout the entire body such as lymphnodes, liver, lungs & spleen[4].

Several lines of evidences suggests that the viral GP plays a key role in manifestation of Ebola virus infection. The transmembrane form of GP targets the Ebola virus to cells that are relevant for its pathogenesis. Specifically GP allows the virus to introduce its contents into monocytes and/or macrophages, where cell damage or exposure to viral particle may cause the release of cytokines [8] which damages vascular integirty [9]. Thus sGP may alter the immune response by neutrophil activation while the transmembrane GP may contribute to the haemorrhagic fever symptoms by targetting virus to cells of reticuloendothelial network and the lining of blood vessels. GP reduces specific integrins responsible for cell adhesion to the inner cellular structure and damage to the liver, which leads to coagulopathy [4].

Immune response to Ebola virus infection : Ebola virus replicates at an unusually high rate that overwhelms the protein synthesis apparatus of infected cells and host immune defenses . Both the adaptive immune and inflammatory system respond to infection at the same time[10].

Laboratory diagnosis : Early laboratory diagnosis/confirmation of suspected clinical hemorrhagic fever case is essential to implement appropriate control measures.

The virologic and immunologic consequences of EHF are different in acute, early cases. The presentation of abrupt illness, high fever (>101 F) of less than 3 weeks, no predisposing factors for hemorrhagic manifestations and atleast two hemorrhagic symptoms (e.g. epistaxis, bloody stool or hemoptysis) collect ample of evidence to consider EHF. In addition to clinical symptoms detection of viral antigen by ELISA and RT-PCR are particularly useful, rapid and sensitive tests. Viral antigen can be detectable after 3-6 days after onset of symptoms, but antigen positivity disappears in 7-16 days after symptoms have begun. Disappearance of antigen reflects effective immune response and viral containment [11,12].

Presence of IgM or IgG antibodies for Ebola virus antigen can be detected by various tests like antigen capture enzyme linked immunosorbant assays (ELISA). IgM appears between 2 - 9 days after symptoms starts and disappear between 30 -168 days[3]. IgG appears 6-18 days after onset of symptoms. IgG antibodies persist for many months. Indirect fluorescent antibody detection tests are easy to perform but lack specificity and may give false positive results [11,12]. The virus can also be cultured

safely. In 1995, Dr. Sherif Zaki of CDC has devised a colorimetric test that can identify Ebola virus in formalin preserved skin biopsies from fatal cases of suspected EHF infection.

Formalin inactivates the virus, rendering the specimen safe for transport and obviating the need for special laboratories. Results can be available in 24 hours. Although the samples must be taken posthumously, this diagnostic immuno-histo chemical test could prove to be reliable surveillance device in the field when EHF is suspected. The CDC made skin biopsy kits available but requires all specimens to be sent to the United States for analysis[5].

Since 1994 the incidence of Ebola outbreaks has increased and as a consequence, the awareness of the disease has improved and facilities capable of diagnosis of EHF were established in Africa [2].

National Public Health Laboratories in endemic countries like Uganda (UVRI), Kenya (KEMRI), & Gabon (CIRMF) have already developed capacities of diagnosis by ELISA and RT-PCR. South Africa is the only African country with maximum containment enclosed suit laboratories where all class 4 pathogens can be handled safely[2].

Vaccines : No vaccine is currently available for humans. However, DNA vaccines derived from adenoviruses, vesicular sotmatitis Indiana virus (VSIV) or Filovirus-like particles (VLPs) could protect nonhuman primates from Ebola - induced disease. DNA vaccines, adenovirus - based vaccines, and VSIV-based vaccines have entered clinical trials.

Management : There is no FDA-approved antiviral treatment for EHF [11,12]. Supportive management palliative care has to be practiced. All patients require close supervision and/or intensive care support. Supportive management of infected patients is primarily followed with special attention towards maintenance of hydration, circulatory volume, blood pressure and provision of supplemental oxygen. Injections, catheters and parenteral interventions must be minimized to avoid trauma [13,14]. Patients with Ebola fever presenting with hypotension and shock are difficult to manage. The administration of intravenous fluids can easily evolve into pulmonary edema. Thus, as anguineous fluids should be used judiciously[15].

Management of bleeding is controversial. Mild bleeding should not be treated when there is no evidence of DIC. On the other hand it has been advocated that DIC should be treated prophylactically through the replacement of coagulation factors and platelets. Heparin therapy should commence after laboratory confirmation [15].

Control measures : Interrupting the viral transmission chain is of utmost importance in controlling an outbreak of EHF. Strict public health measures need to be implemented as quickly as possible. This includes isolation of patient, barrier precaution and identification and tracking of all contacts. Stringent infection control practices by bed side nurses and all levels of health care providers are critical.

Infection control techniques should include :

- Use of protective clothing featuring masks, gowns, and double gloves; Hand washing with disinfectant rinse followed by soap and water; Patient isolation;
- Autoclaving or disinfecting of all contaminated materials with bleach; Needle precautions;
- Proper containment, disinfection and disposal of biohazardous materials; Appropriate labeling of specimens & Strictly limited access to patients.

Most of the time, outbreaks are managed by a core structure called the International Committee on Scientific and Technical Coordination, under the aegis of the World Health Organisation (WHO). The committee is in-charge of implementing control measure activities on daily basis[3] the WHO have developed a manual detailing procedures that reduce the risk of transmission which can be accessed at www.cdc.gov/ncidoc/dvrd/spb/mnpages/vhfmanual.htm [13,14,16].

Conclusion : To conclude, Ebola hemorrhagic fever outbreaks are becoming very frequent in Africa. Knowing more about this deadly agent, especially regarding the attributes like its etiology, transmission, clinical picture, pathophysiology, immune response, laboratory diagnosis & management may help to overcome it. Control measures hold the most important place in management of outbreaks.

Last but not the least, the mid-August 2014 outbreak with 1,145 deaths (numbers may be vastly underestimated according to the WHO), the need for a promising vaccine for human use should be the top most priority.

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