Special Focus

Ebola virus outbreak and its management: An overview

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ABSTRACT

Ebola virus disease (EVD) is a severe, often fatal disease in humans and nonhuman primates (such as monkeys, gorillas, and chimpanzees). The current outbreak is in West Africa involving countries of Guinea, Liberia, Sierra Leone and Nigeria (as on August 6, 2014). The infection is transmitted to humans through close contact with the blood, secretions, organs or other body fluids of infected nonhuman primates. Clinically, patient should be diagnosed based on signs and symptoms with history of travel from Ebola affected areas or exposure to EVD patients. All suspected patient should be investigated for IgM (enzyme-linked immunosorbent assay), antigen detection, and reverse transcriptase-polymerase chain reaction to confirm. Currently, no specific therapy is available that has demonstrated efficacy in the treatment of EVD. In the absence of specific therapy, a number of modalities have been tried. General medical support is critical. Steriod therapy has no role. There is no role for antibiotics unless there is evidence of secondary bacterial infection. Nutrition is complicated by the patient's nausea, vomiting, and diarrhea. Good hydration is to be ensured with good amount of protein supplement. Experimental vaccines are under trial.

Key words: Ebola virus disease, management, outbreak, West Africa, World Health Organization

INTRODUCTION

An ongoing epidemic of the Ebola virus disease (EVD) in West Africa is the most severe Ebola virus (EBOV) outbreak recorded in regard to the number of human cases and fatalities.[1] The outbreak which began in Guinea in December 2013 remained undetected until March 2014, after which it spread to Liberia, Sierra Leone, and Nigeria.[2] World Health Organization (WHO) as of August 9, 2014 reported a total of 1,848 suspected cases with 1,013 deaths, of which 1,176 cases and 660 deaths have been laboratory confirmed to be Ebola.[3] On August 8, 2014, WHO declared the outbreak a public health emergency of international concern.[4] Various organizations, including the Economic Community of West African States, US Centers for Disease Control and Prevention, and the European Commission have donated funds and mobilized personnel to help counter the outbreak; charities are also working in the area.

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AGENT AND OUTBREAKS

Ebola first appeared in 1976 in two simultaneous outbreaks, in Nzara, Sudan, and in Yambuku, Democratic Republic of Congo. The latter was in a village situated near the Ebola River, from which the disease takes its name.[5] EVD formerly known as Ebola hemorrhagic fever (EHF) is the most fatal human disease encountered so far having a case fatality rate up to 90%. EVD is caused by four of five known highly pathogenic virii classified in the genus EBOV, family Filoviridae, order *Mononegavirales*. These four viruses are Bundibugyo virus, Sudan virus, Taï Forest virus, and EBOV. The fifth virus, Reston virus, appears less capable of causing

disease in humans than other Ebola species. Formerly designated as Zaire Ebola virus (ZEBOV), EBOV is the most dangerous of the five known virii within the genus EBOV. The present outbreak in West Africa is by the ZEBOV.

TRANSMISSION

Fruit bats are believed to be the carrier of this infection, which spread the virus without itself being affected.[6] Transmission has been reported from "bushmeat" of primates, forest antelope, wild pigs, and bats. In Africa, infection has been documented to have been transmitted through handling of infected animals found ill or dead or in the rainforests. EVD has been reported to spread in the community through human-to-human transmission with infections resulting from direct contact with blood or bodily fluids from an infected person or by contact with contaminated medical equipment, particularly needles and syringes. Men who have recovered from the disease can still transmit the virus through their semen for up to 7 weeks after recovery from illness. Transmission through oral exposure and through the conjunctiva exposure is likely and has been confirmed in nonhuman primates. Inappropriate protective clothing of health care providers may also contract the disease. Hospital-acquired transmission has been earlier reported in African hospitals due to the reuse of needles and lack of universal precautions. Airborne transmission though has not been documented during previous EVD outbreaks; they are, however, infectious as breathable 0.8-1.2 μm laboratory generated droplets.[7] Recently the virus has been shown to travel without contact from pigs to nonhuman primates. Exposure to EBOVs can occur in health care settings where hospital staffs are not wearing appropriate protective equipment, such as masks, gowns, and gloves. Proper cleaning and disposal of instruments, such as needles and syringes, is also important. If instruments are not disposable, they must be sterilized before being used again. Without adequate sterilization of the instruments, virus transmission can continue and amplify an outbreak.

PATHOGENESIS

The major targets of this infection are endothelial cells, mononuclear phagocytes, and hepatocytes where a full-length transmembrane form or secreted glycoprotein (sGP) known as the EBOV glycoprotein (GP) is synthesized after infection. EBOV replicates at an unusually high rate that overpowers the protein synthesis apparatus of infected cells and host immune defenses.[8] The GP is forming trimeric complex binds the virus to the endothelial cells lining the interior surface of blood vessels. This preferential binding of EBOV GP to the endothelium was demonstrated by use of two independent methodologies involving fluorescence-activated cell sorter analysis, and pseudotyping experiments. The sGP forms a dimeric protein that interferes with the signaling of neutrophils allowing the virus to evade the immune system by inhibiting early steps of neutrophil activation. These white blood cells also serve as carriers to transport the virus throughout the entire body to places such as the lymph nodes, liver, lungs, and spleen. The presence of viral particles and cell damage resulting from budding causes the release of cytokines like tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-8 and others which act as signaling molecules for fever and inflammation. During an infection, there is evidence that both host and viral proteins contribute to the pathogenesis of EBOV. Increases in the levels of inflammatory cytokines interferon (IFN-g), IFN-α, IL-2, IL-10, and TNF-α were associated with fatality from EHF. The virus eventually infects the microvascular endothelial cells and compromises vascular integrity. This loss in vascular integrity is fostered with synthesis of GP, which reduces specific integrins responsible for cell adhesion to the inter-cellular structure, and damage to the liver, which leads to coagulopathy. Severe coagulopathy ultimately leads to death.

CLINICAL FEATURES

Symptoms typically start 2 days to 3 weeks after becoming infected with the virus, with a nonspecific flu-like stage characterized by fatigue, fever, headaches, myalgia, malaise, arthralgia and abdominal pain. Generally nausea, vomiting, diarrhea and loss of appetite follow, along with decreased functioning of the liver and kidneys. Less common symptoms include sore throat, chest pain, hiccups, shortness of breath and trouble swallowing.[9] A maculopapular rash has been described, as have laboratory abnormalities including elevated aminotransferase levels, marked range of range of hematological irregularities, such as neutrophilia, lymphocytopenia, and thrombocytopenia. Cytokines are released when reticuloendothelial cells encounter virus, which can contribute to exaggerated inflammatory responses that are not protective. The incubation period typically lasts 5-7 days, although it can be as short as 2 days and as long as 21 days. In order to make a diagnosis, typically other diseases with similar early symptoms such as malaria, typhoid fever, shigellosis, cholera, dengue, leptospirosis, plague, rickettsiosis, relapsing fever, meningitis, hepatitis and other viral hemorrhagic fevers are first ruled out.[5] To confirm the diagnosis blood samples are tested for viral antibodies, viral RNA, or the virus itself. Bleeding has been mostly reported from puncture sites and mucous membranes of the gastrointestinal tract, nose, vagina and gums. 5-7 days after manifestations of initial symptoms, internal and subcutaneous bleeding may present itself through hematemesis and reddening of the eyes. Bleeding into the skin may create petechiae, purpura, ecchymoses, and hematomas especially around needle injection sites. Heavy bleeding though rare is usually confined to the gastrointestinal tract.[10] Damage to the liver, combined with massive viremia, leads to disseminated intravascular coagulopathy, which is an indicative of worse prognosis,

thereby leading to death. Death due to multiple organ dysfunction syndromes has been reported to occur within 7-16 days after appearance of initial symptoms.

INVESTIGATION AND DIAGNOSIS

Clinical case definition

Suspected case

Patient had history of travel or close contact with symptomatic person traveling from EVD affected areas in the past 21 days, with high grade fever more than 101°F, along with one or more of the following additional symptoms: Headache, body ache, unexplained hemorrhage, abdominal pain, diarrhea, and vomiting.

Confirmed case

A case with the above features and laboratory confirmed diagnostic evidence of EBOV infection at a biosafety level-3 (BSL-3) facility by any one of the following:

- IgM (enzyme-linked immunosorbent assay [ELISA])
- Antigen detection
- Reverse transcriptase-polymerase chain reaction (RT-PCR).

The medical history, especially travel and work history along with exposure to wildlife are important to suspect the diagnosis of EVD. Isolating the virus by cell culture, detecting the viral RNA by PCR and detecting proteins by ELISA is effective early and in those who have died from the disease. Detecting antibodies against the virus is effective late in the disease and in those who recover. During an outbreak, virus isolation is often not feasible;[11] hence the most common diagnostic methods are RT-PCR and ELISA detection of proteins, which can be performed in field hospitals. Electron microscopy helps identification of filovirions from cell cultures. Serum neutralization tests are also carried out. Samples from patients are an extreme biohazard risk and hence testing should be conducted under maximum biological containment conditions.

MANAGEMENT

EBOVs are highly contagious, hence decreasing the spread of the disease from infected monkeys and pigs to human forms a primary preventive measure. Techniques to avoid infection involve not contacting infected blood or secretions, including from those who are dead, suspecting and diagnosing the disease early and using standard precautions for all patients in the healthcare setting. Recommended measures when caring for those who are infected include their isolation, equipment sterilization, hand washing and wearing protective clothing.[12] Samples of bodily fluids and tissues from people with the disease should be handled with special caution. Due to lack of proper equipment and hygienic practices, large-scale epidemics have occurred mostly in poor, isolated areas without modern hospitals or well-educated medical staff. Those requiring embalming of bodies during traditional burial rituals should be discouraged or modified.[13] Airline crews flying to the affected areas of the world are trained to identify Ebola and isolate anyone who has symptoms. Quarantine or enforced isolation is usually an effective measure undertaken to decrease the spread of the disease.[14] EBOVs are WHO risk group 4 pathogens, requiring BSL-4-equivalent containment. Laboratory researchers must be properly trained in BSL-4 practices and wear proper personal protective equipment (PPE).

Case management in a hospital

- Isolate the patient;
- Patients should be cared in a single room (preferably an airborne infection isolation room);
- Follow standard precautions including appropriate PPEs, for example, disposable water repellent cap, water resistant gown, surgical mask/N95 respirator, face shield/goggles, gloves, and shoe covers/boots;
- Avoid aerosol generating procedures;
- Environmental cleaning and disinfection;
- Proper disposal of potentially infected material following biohazard precautions; and
- Reporting and notifying to health authority.[15-17]

Since 1976 more than 15 Ebola outbreaks have flared in sub-Saharan Africa, yet therapeutic alternatives remain undeveloped. No EBOV-specific treatment exists. Treatment is primarily supportive in nature and includes minimizing invasive procedures, balancing intravenous fluids and electrolytes with oral rehydration to counter dehydration, administration of anticoagulants early in infection to prevent or control disseminated intravascular coagulation, administration of procoagulants late in infection to control bleeding, maintaining oxygen levels, pain management, and the use of medications to treat bacterial or fungal secondary infections.[5] Early treatment may increase the chance of survival. There are no licensed vaccines or specific antiviral or immune-mediated treatments for ill-patients or for post exposure prophylaxis, though the most promising prospects are DNA vaccines[18] or vaccines derived from adenoviruses, vesicular stomatitis Indiana virus or filo virus-like particles as these vaccines have protected the nonhuman primates from Ebola-related disorders. A number of experimental treatments are being studied. Antibody titers against EBOV GPs are readily detectable in patients who recover from EBOV infection; however, reports state that serum from recovered patients did not consistently protect against infection or exhibit neutralization of virus replication in cell culture. Furthermore, passive transfer of antibodies in animal models only delays the onset of symptoms, the overall survival remaining unaltered. Recently, the neutralization of virus replication by selected monoclonal antibodies isolated from the bone marrow of recovered patients was demonstrated *in vitro* and monoclonal antibodies that

recognize specific epitopes of EBOV GP have been shown to confer immune protection in a murine model of EBOV infection and in guinea pigs.[8] However, it is relatively easy to protect against infection in the mouse model, and protection of guinea pigs required a high dose of antibody administered very close to the time of virus challenge. Taken together, these results suggest that antibodies alone do not provide protective immunity in a natural context and that cellular immunity is likely to play a significant role in virus clearance.

OPTIONS FOR PREVENTION AND CONTROL

Visitors and residents in affected areas face a very low risk of infection in the community if precautions are strictly followed:

- Avoiding contact with symptomatic patients and/or their bodily fluids
- Avoiding contact with corpses and/or bodily fluids from deceased patients
- Avoiding contact with wild animals (including monkeys, forest antelopes, rodents and bats), both alive and dead, and consumption of "bush meat"
- Washing hands regularly, using soap or antiseptics.

FUTURE PROSPECTS

The US National Institutes of Health is supporting the first phase 1 clinical trial of a new prototype experimental vaccine expected to begin in September 2014. ZMapp is an experimental serum mixture, composed of three humanized monoclonal antibodies transgenically produced and subsequently grown in large numbers in the tobacco plant Nicotiana in the bio-production process for immunological protection against the EBOV.[19] On July 31, 2014, ZMapp was first tested on humans. Administered to two Americans infected with Ebola, both showed positive results.[20] Other promising treatments rely on antisense technology. Both small interfering RNAs (siRNAs) and phosphorodiamidate morpholino oligomers targeting the ZEBOV RNA polymerase L protein could prevent disease in nonhuman primates. TKM-Ebola, a siRNA compound, is currently being tested in a phase I clinical trial in people.[21]

The recent West African Ebola crisis is unique given the virulence, intensive community and health facility transmission patterns, and weak health systems. The WHO declaration of a public health emergency of international concern triggered temporary recommendations directed to affected states, bordering states and the international community. Sound public health practices, engagement with affected communities, and considerable international assistance and global solidarity will be needed to defeat Ebola in West Africa. An understanding of the mechanisms underlying EBOV-induced cytopathic effects has however facilitated the process of vaccine and antiviral therapy development, which has in turn provided new information about pathogenesis and the immune response. Though EBOV does not exhibit the high degree of variability that other enveloped viruses may employ to evade host immunity, EBOV GP alters target-cell function and thus represents a novel strategy for immune evasion that may have arisen through the evolution of EBOV with its natural host.[8] Alteration of the cell surface expression of adhesion proteins and immune recognition molecules may disrupt processes critical to immune activation and cytolytic-T-cell function. These phenomena likely account for the dysregulation of the inflammatory response and the vascular dysfunction characteristic of lethal EBOV infection, thus providing a rationale for focusing on GP as a target for a preventative vaccine and providing leads for other clinical interventions.

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