Editorial

Ebola virus disease - An update

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In March 2014, the World Health Organization was notified of an outbreak Ebola virus disease (EVD), formerly known as Ebola haemorrhagic fever, in southeastern Guinea in West Africa. The disease subsequently spread to the capital, Conakry, and then to the neighboring countries Liberia, Sierra Leone, Nigeria and Senegal. In August 8, 2014 the WHO declared the epidemic a Public Health Emergency of international concern. The present outbreak has spread rapidly and according to the last report it has infected more than 17,000 people and caused 6070 deaths according to recent report.[1] The case fatality in this outbreak is ranging from 42% to 66%. Good news is that, the transmission was successfully interrupted in Nigeria and prevented in Senegal. In some parts of Liberia there is an evidence for a decrease in transmission of Ebola virus.[2] A significant number of health care workers, including physicians attending the patients have also contracted the disease and some have succumbed to it. As the disease complicates with multiple organ dysfunction requiring intensive care management, the role of intensivist becomes integral in overall management of this condition. Use of personal protective equipment (PPE) is essential while caring for these patients.

Ebola virus belongs to the filoviridae virus family. Ebola virus was first described in an outbreak in the northwest area of the Democratic Republic of Congo in 1976. The first epidemic occurred along the river Ebola and the virus is named after it. This virus is an enveloped nonsegmented RNA virus with a uniform diameter but a wide variation in length.

Ebola virus disease is a classic zoonotic disease with persistence of the virus in a reservoir species in endemic area. Fruit and insectivorous bats are the most likely hosts for the virus but this is not conclusively proven.[3]

Pathogenesis

The Ebola virus enters the host through mucosal or breaks in the skin. Infectious viral particles have been shown in blood, saliva, vomitus, faeces, urine, sweat and even semen and vaginal secretions. The spread from person to person requires direct contact with body fluids. After the entry, the virus initially infects the dendritic cells and macrophages. These cells carry virus to regional lymph nodes where they replicate. The virus can spread *via* blood stream and lymphatic channels to entire body. The Ebola virus has broad tissue tropism and can virtually infect any cell in the body. Inflammatory process results in capillary leak causing intravascular volume depletion. Viral infected macrophages express tissue factor on their cell surface which leads to activation of coagulation cascade and consumptive coagulopathy. Direct viral affection of hepatocytes also contributes for reduction in level of coagulation factors. Haemorrhage related to Ebola occurs late, is usually gastrointestinal but cutaneous and conjunctival bleeding may also be seen.

Clinical presentation

The incubation period of EVD is 2 – 21 days, the average being four to ten days particularly when the

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disease occurs following laboratory or nosocomial exposure[4]. The lack of information regarding onset of symptoms in outbreak regions happens to be the reason for this wide range. The infection with different strains of virus may have variable clinical features. Classically the disease has four phases of illness. They are; early febrile phase (0-3 days), gastrointestinal phase (3-10 days), phase of shock or recovery (7-12 days) and phase of late complications such as secondary infections and neurocognitive abnormalities (more than 10 days). In general, EVD patients typically present with high grade fever along with headache, myalgia, anorexia, vomiting and diarrhoea. The subsequent manifestations of disease are due to multisystem organ involvement. Prostration and severe abdominal pain are common. Neurological manifestations such as altered level of consciousness, seizures and coma are often observed. Worsening of gastrointestinal symptoms with severe large volume diarrhoea leading to hypovolemic shock is a common feature. Overt respiratory failure is not common. Clinically significant haemorrhage is a late manifestation of disease and it occurs in only minority of patients. Massive bleeding is typically isolated to gastrointestinal tract. Purpura, petechiae, conjuctival haemorrhage and oozing from venipuncture site are described in few cases. Most of deaths occurred between days 7 and 12 of illness and the cause of death being hypovolaemic shock and multisystem organ failure.[5] Particularly vulnerable populations include children less than 5 years, the elderly and pregnant women. The overall case fatality rate in present epidemic is ranging from 42% to 66%. In nonfatal cases, the clinical improvement begins during day 6 to 11.

Laboratory parameters

Haemoglobin is usually normal but may be elevated in early stages due to dehydration. Leucopaenia with lymphopaenia is often seen. Thrombocytopaenia due to decreased production and consumptive coagulopathy is typically observed. Many reports have described prolonged prothrombin time. Elevation of aspartate and alanine aminotransferase (AST and ALT) to two to three times normal is common. It is usually AST predominant suggesting hypoperfusion of liver. Amylase lipase also may be elevated. Metabolic acidosis is common due to diarrhoea and elevated lactate secondary to hypoperfusion. Severe hypokalaemia following profound diarrhoea has been described.

Diagnosis

The gold standard for diagnosis of EVD is real-time polymerase chain reaction (RT-PCR). Antigen detection by enzyme-linked immunosorbent assay can also be used.

Management

Before encountering a possible outbreak, each hospital should have a plan in place that specifically covers where these patients will be cared for and who will be caring for them. Availability of PPE and protocols for using it should be checked. We need to strike a balance between being appropriately cautious and being scared. According to an emergency physician treating ebola patients at Liberia, we "should respect the virus, but don't fear it".[6] Adequate precautions should be taken to lessen the chances of health care workers getting infected.

Patient with EVD should be managed in single-patient room isolated from other patient care areas. Ideally the room should have negative pressure isolation. The facility to dispose patient's body fluids inside the room should be present. Monitors, suction apparatus, oxygen connection and enough space for life support equipment should be present. Intensive care unit of a hospital would be an ideal place for care of patients with EVD. As few people as possible should be involved in direct care of patient. Healthcare worker must wear disposable water resistant coveralls, impermeable gown, an N95 mask and full face shield, two sets of gloves and foot and leg coverings. It would be ideal to use powered air purifier respiratory suit while performing airway suctioning or intubation. This provides high-efficiency particulate air (HEPA) filtering as well as fresh air to clinicians.[7] However these suits are expensive, not easily available and it takes more time for donning. PPEs do have some disadvantages. It limits human interactions and hides facial expressions that normally carry empathy and build patient-clinician relationship. Adoption of

PPE not based on known modes of transmission is also a challenge to healthcare workers.

In the setting of major out breaks, rapid clinical assessment must be done to triage the patients into one of three categories: those who are clinically hypovolaemic, not in shock and able to provide self-care; those who are hypovolaemic, not in shock, but unable to provide self-care; and those in shock with evidence of organ failure whose outcome probably would not be altered by medical interventions. The first group who are able to care for themselves have potential for recovery with oral antiemetics, antidiarrhoeal therapy, and adequate rehydration with oral electrolyte solutions. The other two groups of patients would need hospital admission and special attention. The crucial step in management of EVD is aggressive rehydration. The daily fluid loss in critically ill patients infected with Ebola virus can be in range of 5-10 L/day. Most of the clinicians prefer Ringer's lactate as solution for intravenous hydration. Colloid preparations are not recommended in management of EVD. Blood component transfusion should be reserved for patients with clinical bleeding. Hypokalaemia is often seen which has to be corrected by enteral replacement. Intravenous correction is required if the patient has severe nausea and vomiting.

Invasive monitoring

The decision to put the patient on invasive monitoring should be taken carefully considering the benefit to the patient and the risk to healthcare staff. Invasive arterial blood pressure monitoring is definitely useful for patient care but poses significant risk to the attending staff in case of disconnections or leak. A placement of central venous cannula is mandatory which provides a low-risk access to blood samples along with easy delivery of medications particularly if vasopressor drugs are required. While placing a central venous cannula, the procedure should be done by experienced clinician under ultrasound guidance. Non-suture securing devices must be used to reduce potential needle stick injury.

Airway management

Primary presentation as respiratory failure is not common in EVD. However, acute respiratory distress syndrome may be precipitated secondary to shock, fluid overload, respiratory muscle fatigue or transfusion related lung injury. These patients have high incidence of vomiting and haematemesis and hence noninvasive ventilation is not preferred. Endotracheal intubation if required, must be done in an elective fashion to minimise the risk of contamination to caregiver where enough time is given to don the PPE correctly.

Specific therapy

At present, no specific therapy is available for treatment of EVD. Many molecules with different mechanisms of action are been tried in treatment of these patients.[8] An experimental drug, ZMapp which is a combination of three humanised monoclonal antibodies manufactured in tobacco plants with neutralising efficacy against Ebola virus glycoprotein has been tried in some patients with varying success. In fact, it was successfully in nonhuman primates.[9] However, limited supply will not allow its large-scale use. Currently there are no approved antivirals for treatment of Ebola virus. Brincidofovir, an orally available lipid conjugate of cidofovir previously known to be useful against DNA viruses has been tried in few patients in United States. TKM-Ebola is another novel medication, emergency use of which has been approved by FDA in current epidemic.[10] It is a small interfering RNA (siRNA) that 3 of Ebola's 7 proteins. AVI-7537, a molecule which inhibits VP24 protein of Ebola virus is in early stage of development. VP24 protein is very important for virulence of Ebola as it inhibits host interferon signaling. Human convalescent serum from survivors of EVD has been used experimentally. Some drugs which are not antivirals such as chloroquine, statins, clomiphene and amiodarone have been shown to have *in vitro* activity against Ebola virus and may have a therapeutic role in future. No effective vaccine is available, but attempts are on to produce a vaccine. The present research is going on in two vaccine candidates - Chimpanzee adenovirus serotype 3 and recombinant vesicular stomatitis virus.

Summary

The current outbreak of Ebola virus disease is predominantly limited to three West African countries. However, as it is highly transmissible disease, hospitals should be prepared for dealing with this disease and have protocols in place. In resource-limited settings, isolation of sick from population at large is the cornerstone of reducing the transmission. Aggressive use of fluids, antiemetics and antidiarrhoeal medications is the mainstay of therapy. PPEs should be used by healthcare workers for all patient contacts.

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