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Ebola Virus Disease: Current Trends in Clinical Management

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Review Article

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Abstract

Ebola virus disease (EVD) has been a major public health problem right from its first documented outbreak in West Africa approximately four decades ago. It is one of the viral haemorrhagic fevers (VHFs) with a high case fatality rate. Relevant literature published in peer reviewed biomedical journals as well as undocumented experiences in West Africa have shown that a working knowledge of the disease and a high index of suspicion are vital for prompt diagnosis of EVD. Reverse transcription polymerase chain reaction test (RT-PCR test) is the reliable test for the confirmation of a suspected case of EVD. The requisite precautionary measures, clinical interventions and public health education necessary to control an epidemic must be started on time, and continued until the affected geographical area is certified Ebola virus disease-free. Although there are no licensed drugs nor vaccines for EVD at present, owing to the high number of people dying from EVD and its distressing recurrent epidemics, some investigational pharmaceutical agents have been used to treat people infected with Ebola virus, under the frame work of MEURI (Monitored Emergency Use of Unregistered and Investigational Interventions) duly supported by World Health Organization. These drugs include: ZMAPP, Remdesivir, Favipiravir, mAB, REGN3470-3479, and some vaccines currently at advanced stages of development. Ring vaccinations being carried out in the Democratic Republic of Congo have reportedly proved to be effective. These agents and other effective components of the current management of EVD are succinctly discussed in this paper.

Keywords: Ebola Virus Disease; Treatment; Antiviral Drug

Introduction

Ebola virus disease (EVD) has been a worrisome public health problem right from its first documented outbreak approximately four decades ago [1]. It is one of the viral haemorrhagic fevers (VHFs). Other viral hemorrhagic fevers include: Lassa fever, yellow fever, Argentinian haemorrhagic fever, Marburg fever, Rift-

valley fever, and Bolivian haemorrhagic fever [2]. EVD has high case fatality rate. Ebola virus infection occurred first in 1976 in Nzara, South Sudan, and thereafter in Yambuku in the Democratic Republic of Congo [3]. It acquired its name from a river near Yambuku named Ebola. Outbreaks of the disease have since then also occurred in Liberia, Sierra Leone, Guinea, and Nigeria, the Democratic republic of Congo, amongst other nations. Although its major outbreaks have been in Sub-Saharan African countries, a few EVD patients have had to be treated in European and American health institutions [4].

A widely reported EVD outbreak in Nigeria occurred in 2014 in Lagos after an infected person travelled from Liberia to Nigeria to seek medical attention. Eight out of the 20 confirmed cases of Ebola fever arising from that index case died. Nigeria was later certified Ebola disease free in September of the same year following vigorous clinical attention to affected people, public health campaigns using various media of communication, monitoring and follow up of contacts and discharged patients [5].

The 2014 - 2016 EVD outbreaks in West Africa resulted in 28, 616 cases out of which 11,310 people died. Overall case fatalities from 2014-2016 in West African sub-regions ranged from 24% to 65% for people affected in Sierra Leone, Liberia and Guinea [5,6]. At present the latest epidemics in the Democratic Republic of Congo has come under control.

As Ebola virus disease shares similar clinical presentation in its early stage as several other pathological entities such as typhoid fever, malaria, acute hepatitis, and other fevers, a high index of suspicion and knowledge of its presentation are required for its early diagnosis. Early detection then paves the way for early commencement of quarantine and other elements of its rational management. Health workers therefore from time to time need to read reviews of the biology, precautionary measures and current developments in the treatment of EBD, hence this paper.

Virology and Transmission

Ebola virus belongs to the family, Filoviridae which includes three genera of viruses: Ebola, Marburg, and Cueva. The genus Ebola consists of five species which include: Zaire, Bundibugyo, Reston, Taï Forest and Sudan species. Bundibugyo ebola virus, Zaire ebola virus, and Sudan ebola virus have been implicated in the major outbreaks in Africa [3].

Wild animals such as fruit bats, monkeys, antelopes and gorillas are the natural hosts of Ebola virus from which they are transmitted to man. Human to human transmission then continues through contact with contaminated body fluids, and through organ donation. Transmission can also occur by contact with surfaces and materials such as beddings, and clothing contaminated with body fluids from an infected person [7].

Ebola viral particles are still found in human body fluids, including blood and semen, several weeks after a person has recovered from the clinical disease. Human semen could be a vehicle of transmission of the virus for 2 weeks or more after recovery from Ebola virus disease. The incubation period is approximately 2-21 days. Many health workers have contracted the disease while attending to infected patients sometimes resulting in the death of the affected health workers.

Symptomatology

Ebola virus disease is a multi-systemic illness with acute onset of severe headache, myalgia and high grade fever [8]. Other symptoms include generalised skin rashes which usually start from the face, vomiting, diarrhea, vomiting of blood (haematemesis), swelling of the face, and coughing up blood (hemoptysis). Hypovolemia, hypotension, metabolic acidosis, and multi-organ dysfunction may follow. If adequate therapeutic intervention is not instituted the eventual outcome of EVD is frequently death. Definitive diagnosis is made by reverse-transcription polymerase chain reaction (RT-PCR) [9,10].

Strong suspicion of EVD is followed up with firm diagnosis, contact tracing, with quarantine of suspect and isolation of laboratory-confirmed patients with appropriate treatment of the patient in a special ward [11,12].

Current Therapeutic Interventions

Ebola virus disease patients are managed with supportive measures as well as with some therapeutic interventions that are in the process of development. Close monitoring of the patient's clinical progress and observance of precautions to prevent transmission of the disease to other people are key to success in the management of the disease.

Supportive Treatment

Supportive measures include oral rehydration of the patient; parenteral fluid administration where necessary; and the use of analgesics and antimicrobial drugs as the need arises.

Adequate attention is paid to the fluid and electrolyte balance as well as the caloric needs of the patient knowing that vomiting and diarrhea could make the patient unable to meet their daily nutritional requirements via oral feeding and drinking of water, besides the attendant blood loss.

a.**Oral Rehydration**
This is achieved through the use of oral rehydration solution as in cholera epidemics [13]. Dehydration is one of the complications that could arise from vomiting and diarrhea. Oral rehydration is recommended for mild to moderate dehydration.

b. **Parenteral Fluid Administration**
This is indicated for severe dehydration, hypotension, or shock. Intravenous fluids such as 5% dextrose in water, 0.9% normal saline are used for supply of calories and rehydration in such patients. For continuous or significant blood loss, transfusion of blood or appropriate blood products would be indicated [14,15].

c.**Monitoring and Charting of Vital Signs**
Recording of patient's body temperature, blood pressure, pulse rate and respiratory rate are important to monitor the patient's health status and to determine when there is clinical improvement or deterioration. Ideally, the vital signs should be monitored three times daily but the frequency of monitoring could be varied for an individual patient based on clinical status.

d. **Review of Blood Chemistry**
Tests for the estimation of blood glucose, liver function, electrolytes, urea and creatinine are also used for monitoring the clinical status of the patient.

e.**Analgesic Therapy**
Pain could be a feature of Ebola disease. Paracetamol (acetaminophen) and non-steroidal anti-inflammatory agents (NSAIDS) are useful for their analgesic and antipyretic effects. Aspirin (acetyl salicylic acid) is not usually prescribed owing to its anti-platelet adhesion effect [16]. Opioid analgesics could be cautiously used for severe pain.

f. **Antibiotics**
In the case of concurrent bacterial infection, the ideal practice is to commence antibiotics based on sensitivity test results. However under some compelling circumstances, antimicrobial prophylaxis could be commenced empirically pending sensitivity test results, particularly in resource poor settings [17,18].

Antiviral Therapeutic Agents

No antimicrobial agent has been licensed for the treatment of EVD so far. However some investigational pharmaceutical agents have been used for EVD with varying degrees of success under the frame work of the WHO-backed MEURI (Monitored Emergency Use of Unregistered and Investigational Interventions) strategy [19-22]. Some of these products are: ZMAPP, Remdesivir, Favipiravir, mAB, and REGN3470-3479.

g.**Zmapp**
This is an optimized combination of neutralizing monoclonal antibodies. The drug is a tripartite monoclonal antibodies (m1H3, m2G4 and m4G7) produced in two distinct laboratories. Evidence for its safety and efficacy gathered from some clinical trials already done both in animals and man shows that the benefits of its use outweigh the risks of the use of the therapeutic product. Clinical trials are still on-going [23-25]. ZMAPP being a mixture of antibodies confers passive immunity to an individual thus enhancing the immune response [26]. It can also function directly by attacking the virus by disrupting its surface and neutralizing it to prevent further damage [27]. Post EVD exposure ring vaccinations with this product is on-going in the Democratic Republic of Congo.

h. Remdesivir (Gs-5734)
This is an antiviral drug, a mono-phosporamidate pro-drug of an adenosine analog. Results from clinical trials to assess benefits and risks of using Remdesivir for treatment of patients with Ebola Virus Disease have been encouraging. It has also been effective against some other viruses including Marburg virus, respiratory syncytial virus, and Lassa fever virus. It interferes with the activity of viral RNA-polymerases and so inhibits viral protein synthesis [28]. The safety of this candidate drug has been demonstrated in monkey models of EVD.

i. **REGN 3470-3471-3479**
This is a monoclonal antibody drug candidate for further clinical trial to establish or discourage its use for EVD. It binds competitively to Ebola virus glycoprotein. Encouraging data were obtained from trials using non-human primates [29].

j. **Favipiravir or T 705.**
The use of Favipiravir may be considered in select circumstances where use of ZMapp or Remdesivir or REGN 3470-3471-3479 or mAb114 are not available. It is a promising candidate drug that possesses wide spectrum antiviral effect currently undergoing clinical trial for

influenza. Its use in Ebola Virus treatment is still being studied [30,31].

k. **mAb 114**

mAb 114 is a monoclonal antibody currently in early stages of development for clinical use. Data from studies using rhesus macaques models of Ebola infection have shown that it possesses anti-Ebola virus activity. mAb 114 is being studied in a phase I study with healthy subjects. It has been used in the DRC EVD outbreaks and no appreciable toxicities have been reported from the use of the drug in both healthy subjects and patients with Ebola virus infection [32] Clinical studies are still on-going. Adverse effects so far observed are such as are common with monoclonal antibodies: nausea, vomiting, diarrhea, allergic reactions, and skin rashes [28].

l. Other experimental therapeutic agents undergoing pre-clinical and clinical studies for EVD include the following

Agents such as Activated Protein C that address the coagulopathy that occurs in EVD thereby reducing mortality among EVD patients but do not cure EVD [33-36].

Aphidicolin that inhibits B-family DNA polymerases and arrests virus cell cycle at the G1/S border [37].

Phosphoro-diamidate morpholino oligomers (PMOs), third generation synthetic molecules of antisense oligonucleotides, which block mRNA functions.

DNA vaccines expressing either envelope glycoproteins or nucleocapsid proteins [22].

Ebola Vaccine

Investigational vaccine rVSV-ZEBOV is highly protective against Ebola virus infection. Several trials across the globe have demonstrated its safety [38,39]. The vaccine is made up of genetically engineered vesicular stomatitis virus (VSV) which contains Zaire Ebola Virus. Ring vaccination of high risk populations in affected zones had been carried out in the Democratic Republic of Congo during an EVD outbreak. Ring vaccination was restricted to persons above 6 years and to women who were neither pregnant nor breast feeding until more data on safety of the vaccine in various vulnerable sub-populations [40].

Requisite Precautions

Health workers, clinical and non-clinical staff alike, are to observe standard precautions in caring for all patients in all health facilities to prevent disease transmission to healthy people. The precautionary measures include the following:

Hand hygiene including washing of hands with soap and running water or using either an alcohol-based hand rub or soap have been recommended before and after attending to patients; after any contact with potentially contaminated surfaces; and after removing personal protective equipment (PPE). Bleach/chlorine solutions 0.05% may be used for sanitary purposes also [41].

Other measures are: Appropriate personal protective equipment (PPE); Respiratory hygiene; Prevention of injuries from needles and other sharp instruments; safe waste disposal; Cleaning and disinfection of the environment; safe handling of contaminated linens; cleaning and disinfection of patient-care equipment; and recommended sexual practices being abstinence or correct use of condoms until the semen of survivors tests negative on two occasions [41].

Conclusion

Ebola virus disease is one of the viral haemorrhagic fevers associated with high mortality rate. High index of suspicion and knowledge of its clinical presentation are paramount for early detection of the illness. More concerted effort is needed to see to the licensing of effective pharmaceutical products and vaccine for the disease to effectively take the place of the investigational therapeutic intervention being currently used.

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