

Clinical Case Management Guidelines of Ebola Virus Disease (EVD)

1. Introduction

Ebola Virus Disease (earlier known as Ebola hemorrhagic fever) is a severe, often fatal disease in humans and nonhuman primates (such as monkeys, gorillas, and chimpanzees).

EVD is caused by infection with a virus of the family *Filoviridae*, genus *Ebolavirus*. When infection occurs, symptoms usually begin abruptly. The first *Ebolavirus* species was discovered in 1976 in what is now the Democratic Republic of the Congo near the Ebola River. Since then, about 24 outbreaks (1976-2012) have appeared sporadically mostly in Central African countries of Democratic Republic of the Congo (DRC), Gabon, South Sudan, Ivory Coast, Uganda, and Republic of the Congo (ROC). The current outbreak is in west Africa involving countries of Guinea, Liberia, Sierra Leone and Nigeria (as on 6th August 2014).

There are five identified subspecies of *Ebolavirus*. Four of the five have caused disease in humans: Ebola virus (*Zaire ebolavirus*); Sudan virus (*Sudan ebolavirus*); Taï Forest virus (*Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*); and Bundibugyo virus (*Bundibugyo ebolavirus*). The fifth, Reston virus (*Reston ebolavirus*), has caused disease in nonhuman primates, but not in humans. The present outbreak in West Africa is by the *Zaire ebolavirus*.

2. Transmission

Fruit bats are considered to be the natural reservoir hosts of ebola viruses in Africa. Non human primates are the accidental hosts as humans. The infection is transmitted to humans through close contact with the blood, secretions, organs or other body fluids of infected animals like chimpanzees, guerrillas, monkey, fruit bats etc.

When an infection does occur in humans, further spread to humans is through:

- direct contact (broken skin or mucous membranes) with the blood or secretions or organs or other body fluids of an infected person
- exposure to objects (such as needles) that have been contaminated with infected secretions

There is no airborne transmission for EVD.

During outbreaks of EVD, the disease can spread quickly within health care settings (such as a clinic or hospital). Exposure to ebola viruses can occur in health care settings where hospital staff 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.

3. Clinical case definition:-

- (i) **Suspected case** :- Patient having history of travel or close contact with symptomatic person traveling from Ebola Virus Disease affected areas in the past 21 days, with high grade fever more than 101 degrees F, along with one or more of the following additional symptoms:-

- Headache
- Body ache
- Unexplained haemorrhage
- Abdominal pain
- Diarrhoea
- Vomiting

- (ii) **Confirmed case**: A case with the above features and laboratory confirmed diagnostic evidence of Ebola virus infection at a BSL-3 facility by any one of the following:-

- Ig M (ELISA)
- Antigen detection
- RT-PCR

4. Clinical diagnosis

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 Ig M (ELISA), Antigen detection, RT-PCR to confirm. However this test result may not help in the clinical management of the patient. For sample collection, refer to sample collection, storage and transportation guidelines.

For proper care and management patient also should be investigated for liver function test, kidney function test, Electrolytes, Haemacrit, repeated platelet count, Haemoglobin, WBC.

Diagnosing EVD in an individual who has been infected for only a few days is difficult, because the early symptoms, are nonspecific to ebola virus infection and are seen often in patients with more commonly occurring diseases.

5. Case Management in a Hospital

- (i) Isolate the patient
- (ii) Follow standard precautions including appropriate Personal Protective Equipments(PPE)
- (iii) Restrict visitors
- (iv) Avoid aerosol generating procedures.
- (v) Implement environmental infection control measures.
- (vi) Proper disposal of potentially infected material following biohazard precautions.

5.1. Treatment:

5.1.1 Approach Considerations

1. 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/ experimented. None of them have been scientifically validated. Details of such interventions are given in the annexure.
2. General medical support is critical. Such care must be administered with strict attention to barrier isolation. All body fluids (blood, saliva, urine, and stool) contain infectious virions and should be handled with great care.
3. Surgical intervention generally follows a mistaken diagnosis in which Ebola-associated abdominal signs are mistaken for a surgical abdominal emergency. Such a mistake may be fatal for the patient and for any surgical team members who become contaminated with the patient's blood.
4. Survivors can produce infectious virions for prolonged periods. Therefore, strict barrier isolation in a private room away from traffic patterns must be maintained throughout the illness. Patient's urine, stool, sputum, and blood, along with any objects that have come in contact with the patient or the patient's body fluids (such as laboratory equipment), should be disinfected with a 0.5% sodium hypochlorite solution.

5. Steroid therapy has no role.
6. There is no role for antibiotics unless there is evidence of secondary bacterial infection.

5.1.2. Supportive Care

1. Supportive therapy with attention to intravascular volume, electrolytes, nutrition, and comfort care is of benefit to the patient. Intravascular volume repletion is one of the most important supportive measures.
2. For high grade fever patient should be treated with only tablet paracetamol. No other analgesic, antipyretic and in particular aspirin should be given in this case as these drugs may increase chances of bleeding. Tepid sponging should be done repeatedly to bring down the temperature immediately in case of high grade fever.
3. Due to repeated vomiting and diarrhoea patient may present with shock and electrolyte imbalance. With out vomiting and diarrhea patient also may have shock due to capillary leakage and haemo-concentration may be observed in this case. Plenty of oral fluid may be advised in mild hypotensive cases or those who have no vomiting and diarrhea.
4. There may be transient bone marrow suppression and patient may present with leucopenia and thrombocytopenia for which patient may develop bleeding from different sites and may have also superadded infection. Patient should be transfused with platelets when the count is below 20000/cmm or bleeding from any sites irrespective of platelet count.
5. In case of severe shock and vomiting patient may be treated with intravenous fluid with crystalloid or colloid. Intravenous fluid therapy should be carefully monitored to avoid fluid overload as most of the deaths are associated with it due to rapid correction of fluid in severe shock. Blood transfusion may be required in some cases those who have severe gastrointestinal bleeding and shock. Management should include replacement of coagulation factors and heparin if disseminated intravascular coagulation develops.
6. Patient may present with different organ involvement commonly liver and kidney. Patient may present with jaundice due to liver impairment and acute renal failure due to acute tubular necrosis in case of profound shock or direct renal involvement by Ebola virus. Patient may require dialysis in severe case of renal failure.
7. Patient should be carefully managed by gastroenterologist in case of severe liver dysfunction.

8. Patient may require ICU support for breathlessness due to lung involvement or critical condition.
9. High morbidity and mortality is associated with different co-morbid illness, therefore EVD patients should be carefully treated with known case of Hypertension, Diabetes, coronary artery diseases and pregnancy. Patients those who are on Anti-platelet drugs should be temporarily stopped as these drugs may increase chance of bleeding.
10. Co-infection with EVD should be immediately treated with proper antibiotic. In the early stage if co-infection is not treated properly patient may develop sepsis and septic shock which may lead to fatal outcome.

5.1.3. Diet and Activity

Nutrition is complicated by the patient's nausea, vomiting, and diarrhea. Good hydration is to be ensured with good amount of protein supplement.

5.1.4 Recovery

Recovery often requires months, and delays may be expected before full resumption of normal activities. Weight gain and return of strength are slow. Ebola virus continues to be present for many weeks after resolution of the clinical illness. Semen from men recovering from Ebola infection has been shown to contain infectious virus, and Ebola has been transmitted by sexual intercourse involving recovering men and their sex partners. Any individuals who were exposed to infected patients should be watched closely for signs of early Ebola virus disease.

5.1.5 Disposal of Dead Body

Safe disposal of dead body with proper precaution for prevention of transmission of EVD. Ebola virus is present in almost all kinds of body fluid like blood, saliva, urine, vomit, stool, nasal secretion, gastrointestinal secretion. Therefore it is mandatory that one should not come in contact with these kinds of potentially infectious material. Relatives should be counseled properly regarding the mode of transmission of EVD and to adapt safe practice for the disposal of dead bodies. Ritual activities after death should be strictly avoided. Those persons who are dealing with the disposal of dead bodies requires proper protection for prevention of transmission of Ebola virus. Dead body should be packed with impermeable leaky proof body bags for safe disposal and to prevent contamination

of the environment with body fluids. Anyone who has accidentally come in contact with blood or body fluids should be kept under quarantine and observed for 30 days.

6.0 Prevention of Ebola Virus Disease in Hospital settings.

The health care workers are at high risk of acquiring the ebola virus disease if they do not follow universal and contact precautions. Refer to Hospital infection control guideline for preventing infection among health care workers.

Pharmacologic Therapy

1. Nucleoside analogue inhibitors of the cell-encoded enzyme S-adenosylhomocysteine hydrolase (SAH) have been shown to inhibit *Zaire ebolavirus* replication in adult BALB/c mice infected with mouse-adapted Ebola virus. Inhibition of SAH indirectly inhibits transmethylation reactions required for viral replication. Treatment response was dose-dependent. When doses of 0.7 mg/kg or more every 8 hours were begun on day 0 or 1 of infection, mortality was completely prevented. Even when the drug was given on day 2, 90% survived.
2. Smith et al found that in rhesus macaques infected with a lethal dose of Ebola virus, treatment with interferon beta early after exposure led to a significant increase in survival time, though it did not reduce mortality significantly. These findings suggest that early postexposure interferon-beta therapy may be a promising adjunct in the treatment of Ebola virus infection.
3. Passive immunity has been attempted by using equine-derived hyperimmune globulins and human-derived convalescent immune globulin preparations. In *Ebolavirus* -infected cynomolgus macaques, use of human recombinant interferon alfa-2b in conjunction with hyperimmune equine immunoglobulin G (IgG) delayed but did not prevent death. Equine IgG containing high-titer neutralizing antibodies to Ebola virus protected guinea pigs and baboons but was not effective in protecting infected rhesus monkeys.

During the 1995 outbreak in Kikwit, DRC, human convalescent plasma was used to treat 8 patients with proven Ebola disease, and only 1 patient died. Subsequent studies could not demonstrate survival benefit conferred by convalescent plasma products. The survival of these patients suggests that passive immunity may be of benefit in some patients.

4. Four laboratory workers in Russia who had possible Ebola exposure were treated with a combination of a goat-derived anti-Ebola immunoglobulin plus recombinant human interferon alfa-2. One of these patients had a high-risk exposure and developed clinical evidence of Ebola virus infection. All 4 patients recovered.
5. A recombinant human monoclonal antibody directed against the envelope glycoprotein (GP) of Ebola virus has been demonstrated to possess neutralizing activity. This Ebola virus-neutralizing antibody may be useful in vaccine development or as a passive prophylactic agent.
6. DNA vaccines expressing either envelope GP or nucleocapsid protein (NP) genes of Ebola virus have been demonstrated to induce protection in adult mice exposed to the virus. These vaccines were administered by coating gold beads with DNA expressing the genes for either GP or NP, and they were delivered by skin particle bombardment using a PowderJect-XR gene gun. Both vaccines induced

measurable antibody responses detected by enzyme-linked immunosorbent assay (ELISA) and induced cytotoxic T-cell immunity.

7. Other experimental therapies that use available drugs, though not approved by the US Food and Drug Administration (FDA) for treatment of Ebola virus infection, may be considered. Agents that may reduce mortality without directly effecting viral replication include activated protein C—and a recombinant nematode anticoagulant protein (NAP) that inhibits activated factor VII-tissue factor complex. NAP resulted in attenuation of the coagulopathy associated with decreased fibrinolysis and fibrin deposition with a resultant decrease in the severity of the systemic inflammatory response syndrome.
8. In a rhesus macaque model of Ebola hemorrhagic fever, which carries a mortality approaching 100%, Geisbert et al administered recombinant nematode anticoagulant protein, a potent inhibitor of TF-initiated coagulation.—One third of the monkeys given the nematode anticoagulant protein survived a lethal dose of Ebola virus, whereas 16 of the 17 (94%) control animals died.